Neurological Disorders and Therapeutics

Research Article ISSN: 2514-4790

Alzheimer's disease syndrome – Recognizing the complexity of dementia

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Abstract

Therapies designed to disrupt amyloid plaque deposits or prevent their formation have yielded disappointing results against cognitive failure, suggesting that both our mechanistic models of dementia and interventions must become more nuanced. These treatments targeted Aβ40/42, but the amyloid accumulated in Alzheimer's disease patients is modified extensively and far more structurally diverse. Despite intensive work, the structure and physical state of the most toxic amyloid species remains mysterious. In addition, multiple lines of evidence suggest the genesis and progression of dementia is more complicated than the accumulation of senile plaques beyond a tolerable threshold. If amyloid plays key, but non-exclusive, roles in dementia pathogenesis this hypothesis must be addressed through investigations that are more holistic in scope. New imaging methods provide investigators unprecedented capabilities to detect and classify neuropathology in living subjects. Interpreting future clinical trial outcomes will hinge on correlating effects against dementia in subject cohorts that are precisely differentiated with respect to neuropathology and neurochemistry. Improving understanding of the comorbidities and the environmental/lifestyle factors foreshadowing cognitive failure will aid in the interpretation of clinical trials. Most important, as we seek an elusive cure for AD, these findings may be rapidly translatable into concrete and achievable public health improvements.

Introduction

The notable accumulation of amyloid-β (Aβ) peptides in Alzheimer's disease (AD) brains led to the postulation of the amyloid cascade hypothesis. Profuse amyloid plaques in demented subjects and studies of early-onset Alzheimer disease (EOAD) genes provided strong experimental supporting evidence for the amyloid cascade hypothesis. However, disrupting Aβ deposits or preventing their formation have, so far, not yielded commensurate impacts against dementia in clinical trials. The almost exclusive focus on the amyloid cascade hypothesis inadvertently left systematic studies of comorbid conditions, environmental, lifestyle and psychosocial influences on dementia comparatively unexplored.

The amyloid cascade hypothesis has dominated the field for over two decades. Although amyloid plays an important role in the pathogenesis and clinical course of AD, interventions against Aβ have had only limited impacts against dementia. Despite the translational frustrations, the thorough investigation of amyloidosis in the ambit of AD has provided profound insights into the understanding of the mechanistic impacts of Aβ on dementia development. We offer a succinct description of the present status of late onset Alzheimer's disease (LOAD) research and its nosology in relation to the amyloid hypothesis. In addition, we make reference to synergistic and/or alternative groups of abnormal pathological options in view of the disappointing therapeutic attempts to interfere with the clinical course of LOAD. At present, some of these pathogenic alternatives have not been sufficiently studied to enable the development of robust hypotheses. Such is the case of environmental, lifestyle and psychosocial factors which have been mainly based on correlative observations but have potential for future preventative and therapeutic interventions. On the other hand, the contribution of cardiovascular system dysfunctions and the endocrine biochemical disturbances created by diabetes type-2 have been sufficiently investigated to warrant their participation in the pathogenesis and pathophysiology of LOAD.

While amyloid seems to play critical role(s) in LOAD, there are multiple routes to dementia that do not necessarily involve amyloid deposition. We call for a more expansive view of dementia pathogenesis and its multifactorial instigators and suggest that studies of these factors are about to be augmented by a better understanding of age related comorbidities and exogenous risks factors impacting LOAD etiology. Advances in imaging technologies as well as improved knowledge of potential biochemical pathways leading to neurodegeneration coupled with data processing innovations promise to revolutionize our understanding of the intricate and complex pathogenesis of LOAD. New methods may ultimately confer capabilities to distinguish dementia arising through distinct pathways enabling their more refined nosological classification and the development of precision medicine.

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Key words: *Alzheimer's disease, late-onset Alzheimer's disease, early-onset Alzheimer's disease, amyloid, amyloid precursor protein, dementia, immunotherapy, systemic co-morbidities, non-amyloid pathology.*

Received: July 15, 2017; **Accepted:** August 09, 2017; **Published:** August 12, 2017

Viewing dementia in broader context

Clearly defined mutational events in *APP, PSEN1, PSEN2, tau,* α-synuclein and *APP* gene duplications are directly responsible for genetically determined neurological disorders. Late onset Alzheimer's neurodegeneration, on the other hand, results from the summation of genetic predisposition, epigenetic modulation and multiple brain and aging-associated systemic declines as well as from the negative contribution of environmental toxins, damaging lifestyles and negative psychosocial influences. Mutations or age-related molecular conformational changes that propagate misfolded molecules add to the long list of age-associated pathological events terminating in neuronal degeneration and brain vascular malfunction. The participation of a mélange of pathological events have been primarily classified on the bases of their clinical manifestations and most prominent pathological lesions. However, the neuropathological lesions associated with neurodegeneration are present in variable densities and unique combinations that complicate their classification. It is also evident that besides the presence of amyloid there are other independent systemic and cellular mechanisms in LOAD pathogenesis [1].

Diverse routes to dementia

After 25 years of research guided by the amyloid cascade hypothesis we cannot explain why some individuals with LOAD harbor profuse amyloid deposits while others either entirely avoid this situation or have a limited number of these lesions. What unique history triggers these outcomes? Is amyloid deposition an essential rescue operation that ensures brain survival and prolongs life or is it an accident of nature that disseminates a rogue molecule that spreads and destroys the brain? These pressing and obvious questions have not yet been entirely resolved.

The variable clinical signs and symptoms of LOAD dementia may be the consequences of a collection of conditions and neuropathologically distinct diseases [2]. Although LOAD is formally confirmed after postmortem evaluation of brain amyloid plaque deposition and intracellular neurofibrillary tangle (NFT) accumulation, demented subjects often harbor heterogeneous conglomerations of cerebrovascular and other pathological lesions [3-10]. Advancing age is recognized to be the most significant risk factor for LOAD, but the relationship between neuropathology and dementia in the elderly is not a simple one [11]. Nonagenarian subjects harboring heavy amyloid plaque burdens offer an important insight into dementia etiology. The indistinct demarcation between LOAD and non-demented oldest-old groups in terms of Aβ-related pathological and biochemical features suggests involvement of other significant factors in neurodegeneration and cognitive failure [12].

Recognizing the relatively weak correlations between fibrillar amyloid levels and dementia, investigators have postulated the most neurotoxic entities are soluble Aβ oligomers [13-17]. However, the mechanism producing a transition to toxicity is unclear as Aβ peptides are normal constituents of brain, cerebrospinal fluid, plasma and other peripheral tissues. Moreover, Aβ42 toxicity is only evident *in vitro* at concentrations thousands of fold greater than present *in vivo* [13]. Detailed examination of the molecular constitution of the Aβ species present in LOAD exposes additional complexities. These amphipathic highly reactive Aβ molecules are subjected to extensive posttranslational modifications [18-37] and proteolytic degradation with altered solubility, chemical reactivity and biophysical properties. These alterations also lead to a propensity for Aβ to dimerize and form larger oligomers [38-53]. In addition, subtle posttranslational conformational alterations can produce distinct Aβ strains with toxic prion-like properties [54]. Analogous to prion diseases, although non-infectious, AD amyloid pathology has long been recognized to be transmissible through Aβ seeding protocols into experimental rodents [55,56].

Several authors have challenged the supremacy of the amyloid cascade hypothesis implying that the presence of plaques is neither necessary nor sufficient to yield dementia [15,57-62]. Although Aβ is linked to LOAD, it may be an error to view it as the sole causative agent [57,63]. The prevailing view of LOAD dementia as caused by a succeeding series of consequential events initially precipitated by amyloid accumulation [64] seems poised to become more nuanced and mechanistically complex.

Less attention has been devoted to the possibility that other APP proteolytic fragments, which are presumably also elevated such as the Aη-α proteolytic fragment of APP that inhibits hippocampal neuronal activity, may play a prominent role in the pathogenesis and progression of LOAD [65]. In addition, the APP N-terminal peptide/DR6 receptor interaction [66], APP δ-ɣ fragment [67,68], APP C-terminal peptides CT99/CT83 [69], Jcasp, P31 and the Aβ-related P3 [70] are neurotoxic or provoke neuronal apoptosis. Our preliminary observations suggest that in LOAD putatively toxic CT99/CT83 peptides, rather than Aβ, accumulate abundantly in cellular membranes as if they were not processed by the ɣ-secretase. Furthermore, increased levels of AICD can cause hippocampal mossy fiber sprouting, neuronal hypersensitivity to stress and silent seizures [71]. Duplication of the *APP* gene results in ~50% increased production of Aβ causing EOAD with cerebral amyloid angiopathy [72] similar to the situation observed in Down's syndrome [73]. Elevation of the multiple APP-derived peptides may have some disadvantageous metabolic effects and participate in neurodegeneration through pathways independent from amyloid accumulation.

Expanding the nosology of AD related neurodegeneration

New imaging methods have drawn attention to complexities in the relationship of neuropathology to dementia. Although persuasive evidence suggests amyloid positivity is correlated with dementia development [74] other observations indicate separate pathways to neurodegeneration exist [75] which do not necessarily involve amyloid deposition. Studies of younger Dominantly Inherited Alzheimer Network (DIAN) EOAD mutation carriers revealed amyloid deposition is an early event in the progression of neurodegeneration [76]. However, the situations in subjects with spontaneously emerging neurodegeneration and dementia are more complicated. Imaging studies have revealed a class of cognitively normal subjects exhibiting biomarkers of neurodegeneration in the absence of detectable amyloid deposits designated suspected non-amyloid pathology (SNAP) [77]. A significant minority (25%) of the cognitively normal subjects examined in a population-based sample of elderly individuals were categorized as SNAP. Furthermore, a substantial number of elderly individuals labelled as primary age-related tauopathy (PART) harbor frequent NFT in the medial temporal lobe, basal forebrain, brainstem, olfactory bulbs and cortex without amyloid plaque deposits. Clinically these PART individuals exhibited cognitive function ranging from normal to severely impaired [78]. Additional longitudinal studies will be required to establish whether all PART subjects are destined to develop amyloid deposits and LOAD with the passage of sufficient time.

It is possible that imaging methods are comparatively insensitive to incipient amyloid deposits. However, a study of subjects clinically

diagnosed with mild to moderate LOAD [79] revealed a SNAP-like subgroup with cortical soluble and insoluble Aβ levels that were low or fell below ELISA detection limits. These results undermine attempts to explain LOAD dementia as a simple and direct consequence of the presence of soluble or aggregated toxic amyloid species. Further, they reveal that the standard model of LOAD progression [80] in which amyloid accumulates relentlessly for years and precedes the appearance of NFT and dementia is not universal. The data confirm the earliest phases of LOAD, the point deemed critical for preventative therapeutic intervention, is both poorly defined and neuropathologically complex.

The recent discovery that brain hypometabolism and atrophy sometimes precede amyloid deposition suggest that normalcy and LOAD are more precisely differentiated by the presence of biomarkers of neurodegeneration [81]. A comprehensive reassessment of discreet AD neuropathological and neurodegeneration biomarkers in the context of NIA-AA clinical criteria has been recently published [82]. The new scheme opens the possibility for the selection of more precisely defined cohorts for future clinical trials. The addition of other biomarkers such as those involving vascular, endocrine and immune disturbances will further refine the nosology of what we currently designate as AD. A meticulous accounting of biomarker status and correlation with cognitive function may help clarify whether anti-amyloid therapy would be most beneficial to only a subclass of dementia patients.

Transgenic mice do not produce the biochemically complex pathological events exhibited in human AD [83-85], perhaps explaining why the identical therapeutic interventions have been consistently far more effective in animals than cognitively impaired trial participants. Moreover, these observations reveal the pathophysiology and clinical changes observed in LOAD are the culmination of unique and complicated human disease processes, impossible to model fully in experimental animals.

The experiences of AD interventions

Immunotherapy and other amyloid diminution strategies that proved successful in transgenic mice [86] have yielded limited beneficial outcomes against AD in clinical trials. For a detailed description of these clinical trials and their results the reader is referred to the comprehensive reviews published in the Alzforum database (http://www.alzforum.org/therapeutics). The combined body of evidence from these disappointing efforts to halt AD dementia has led to concerns that the amyloid hypothesis [87,88] must be reevaluated [89] or is channeling the field into unproductive therapeutic directions [15,62].

Some of the strongest evidence directly implicating amyloid in dementia instigation is genetic; mutations in *PSEN* and *APP* genes, as well as *APP* gene duplications, lead to what we defined as EOAD. Despite these links and detailed molecular characterizations, it is not possible to specify the role(s) played by amyloid and other APP fragments in AD [90-91] nor, given the enormous list of critical γ-secretase substrates, is it clear how *PSEN* mutations produce neurodegeneration. Presenilin gene conditional knockout mice exhibit reduced Aβ production and increased inflammatory reactions [92] and detailed examination of *PSEN* mutations has revealed unexpected diversity in the corresponding impacts on Aβ production [19,93-98]. It is now clear that the pathologic and clinical effects of these mutations are impossible to match with simple notions of enhanced production of Aβ42 or altered Aβ40/Aβ42 ratios. Noting that amyloid production is not necessarily required for AD prompted the proposal of the PSEN hypothesis [99] in which the partial loss of *PSEN* gene function provokes neurodegeneration and AD pathology. This model predicts that inhibition of γ-secretase would actually aggravate dementia [100].

It is noteworthy that a large-scale clinical trial of the γ-secretase inhibitor semagacestat was terminated when analysis revealed the subjects were experiencing accelerated cognitive function declines and other serious adverse events such as cancer [101]. Although failing to achieve the desired clinical endpoints, the trial might provide fresh insights into the mechanism of dementia production through the biochemical activities of PSEN. Postmortem neuropathological and neurochemical evaluations of trial participants may help clarify the nature of treatment responses and expose the existence of any common patterns. A comprehensive results report [101] revealed 26 subjects receiving semagacestat expired during the clinical trial. Detailed postmortem biochemical investigations of this participant subgroup, in particular, will be extraordinarily important, but 5 years after the trial termination only a single assessment has been published [102]. Other clinical trials involving the γ-secretase inhibitors were also halted due to undesirable side effects [103,104]. In spite of these frustrations controlling Aβ production by modulating the activity of the β- and γ- secretases is being actively pursued (see Alzforum database: http://www.alzforum.org/therapeutics).

Immunotherapy interventions to mitigate AD dementia have been predicated on the assumption that unmodified Aβ deposits are the prime targets. The clear biochemical complexity of Aβ peptides in AD and the comparatively vague understanding of their functions raise the unsettling prospect that interventions have not succeeded in changing the clinical course of dementia because they were targeted inappropriately or the clinical trials were incorrectly designed [105-108]. However, a precise deconvolution of immunotherapy clinical trial data revealed some encouraging results that were initially obscured due to grouping together subjects in the treatment cohort with different levels of individual clinical conditions coupled with large patient dropouts from the placebo group. However, recent results indicate that the use of monoclonal antibodies in large phase-3 clinical trials comprising individuals with mild LOAD failed to meet their primary end-points (http://www.alzforum.org/therapeutics). In general, these observations suggest that independent of amyloid accumulation other pleiotropic dysfunctional molecules, perturbed biochemical pathways and/or systemic comorbidities are involved in the evolution of LOAD neurodegeneration.

The primary amino acid sequence of APP has been highly conserved through evolutionary history suggesting an underlying functional importance for both the intact molecules and its proteolytically processed derivatives [109-111]. Although AD is defined on the basis of plaque and tangle neuropathology, considered in a broader evolutionary context it is difficult to assign unambiguous pathologic effects to amyloid deposits [112]. Brain amyloid deposition is linked to aging and dementia in humans as well as other mammals including canines and primates, but these animals lack NFT and are incomplete LOAD models [113].

Several investigators speculate that soluble oligomeric Aβ represent the most neurotoxic species in AD while more massive amyloid deposits are comparatively benign [13-17]. This suggests the sudden and complete disruption of amyloid deposits may be detrimental by unleashing toxic species as well as eliciting vasogenic edema and microhemorrhages [114,115] aggravating neuroinflammation. Examination of the aftermath following active immunization suggests that mobilized Aβ remained trapped in the brain [116-119]. Passive

immunization with humanized monoclonal antibodies against Aβ exhibited adverse effects, which were exacerbated in subjects with *APOE* ε4 genotypes [120]. These deleterious effects may result from disruption of vascular amyloid deposited to seal breaches in the blood-brain barrier [90], blocking the presumed antimicrobial activity of Aβ [121,122], interference with the heavy metal chelating ability of Aβ [123-124], meddling with the vasoconstriction induced by Aβ/endothelin-1 activity [125,126] or disturbing Aβ-mediated glucose-fatty acid energy metabolism [127]. Fresh approaches toward the design of Aβ active vaccinations, that include enhanced immunogenicity, may provide effective and affordable AD mitigation [128]. Besides assessing age, gender, personal and family clinical history, it may be necessary to adopt more holistic diagnostic and enrollment criteria which include general evaluation of cardiovascular, endocrine, immune and other systemic and metabolic dysfunctions as well as environmental and lifestyle factors [129-131].

Cardiovascular dysfunction and diabetes in AD pathogenesis

The pathogenesis and pathophysiology of LOAD may be complicated by systemic diseases and environmental factors such as cardiovascular dysregulation. Cardiovascular system disease or natural aging of the heart and vessels, and brain microcirculation may result in regional or global brain perfusion insufficiency with consequent negative effects on cognitive capacities [132]. The brain consumes disproportionate amounts of oxygen and has no energy reserves making an adequate blood supply crucial to proper function [133]. Regional brain activity levels may be inferred by detecting rapid changes in blood oxygenation levels (BOLD) which are presumed to reflect neuronal and associated tissue metabolic responses to stimulation [134]. Recent analyses have revealed an association between intracranial atherosclerosis and LOAD dementia [3-10], and significant correlations between neuropathology and cognition and cardiovascular disease as well as with age-associated cardiovascular performance decline [135-144]. Observations of LOAD subject brain activities reveal marked region-specific metabolic reductions compared to subjects without dementia suggesting both baseline perfusion level declines as well as a loss of surge capacity in response to stimulation [145-149]. An overwhelming body of epidemiologic evidence confirms that LOAD and cerebrovascular disease share common risk factors [150]. New imaging studies have indicated that in some elderly individuals, white matter rarefaction (a surrogate of cerebrovascular insufficiency), brain infarcts and amyloid exert additive effects on cognitive impairment [151]. Intriguingly, what appears to differentiate the oldest-old high pathology control subjects from age-matched LOAD cases is that the former have significantly less white matter rarefaction, less cerebral amyloid angiopathy and fewer NFT than the latter, which suggests less vascular compromise [12]. Recently, an integrative multifactorial data-driven model of LOAD suggested that vascular dysregulation plays a preeminent role in the pathogenesis and progression of this dementia and apparently precedes Aβ manifestations [152].

A substantial fraction of dementia cases harbors a heterogeneous blend of neuropathological lesions and vascular malfunction described as 'mixed' pathology [3,107-110] [3, 153-156]. Although putatively independent of each other [157] these pathological changes do not exist in isolation and using cognitive impairment as a benchmark, it is clear coexisting cerebrovascular malfunction amplifies the deleterious effects of LOAD pathology and accelerates dementia progression [150,157] with important therapeutic implications [158]. Impaired circulation will yield commensurate energy production failure and overall metabolic disturbances and these will have significant consequences for neural function [127]. In addition, the age-associated brain metabolic fueling pathway shifts from glycolysis to ketone body oxidation, reminiscent of hibernation [127,159]. This adjustment may represent an alternative rescue or adaptive function enabling vital neural activities to continue at nominal levels despite suboptimal perfusion and physiological conditions. The complexity of brain physiology coupled with the highly heterogeneous nature of neuropathology may have hindered attempts to mitigate AD dementia using therapeutics focused on amyloid deposit disruption [153].

If circulatory system insufficiency induces or exacerbates AD, restoring blood flow should improve cognitive function [132]. Aggressive medical therapy, artery bypass and stenting methods have been successfully attempted as a means to restore brain blood flow [160-162]. Systematic exploration, of respiratory and cardiovascular disorders related to dysfunctional breathing, lung and heart maladies, hemodynamic dysregulation, arterial stiffness and cerebrovascular disease as well as assessment of the blood-brain barrier (BBB) conditions in relation to cognitive evaluations and treatment of memory impaired patients is long overdue [132,163-168]. New devices to monitor cardiovascular function and blood chemistry on a continuous basis together with imaging-based determinations and ultrasound studies of extant or unfolding AD pathology and cognitive function may offer the potential to undertake proactive dementia preventative and effective measures. A capacity to detect and mitigate the subtle changes heralding increased risk of cognitive failure would be a cost-effective adjunct to the standard treatment approaches.

Subjects with type 2 diabetes are at elevated risk for dementia. This tenet is based on studies suggesting decreased brain insulin and insulin receptors, including insulin-like growth factor and reduced CSF insulin levels. Although these observations have been controversial [169], brain insulin administration enhances memory and cognition in humans [170]. Brain insulin resistance appears to be responsible for grave alterations in energy metabolism and mitochondria dysregulation which could explain amyloid and NFT deposition as well as white matter atrophy, brain microvascular disease, neuroinflammation and glial and neuronal demise [171]. Recent investigations have demonstrated that long lasting insulin ('insulin detemir') administered intranasally improved cognition in individuals with MCI and AD [172]. An ongoing Study of Nasal Insulin to Fight Forgetfulness (SNIFF) is evaluating the effects of insulin on amnestic MCI and early AD individuals. It remains unclear whether insulin dysregulation and hyperglycemia actually cause the pathologic changes of AD [173]. However, vascular damage is prominent in both conditions and chronic diabetes may promote malfunction of the blood-brain barrier associated with AD [174]. Alzheimer disease treatments have focused on eliminating amyloid deposits, but the intricate interrelationship between dementia and diabetes suggests that successful long term mitigation will also necessitate careful management of insulin and glucose levels.

Between now and then – modifying the trajectory of AD dementia while seeking an elusive cure

The long effort toward unraveling the pathologic mechanisms of AD has not yielded therapeutic successes commensurate with the enormous investment of funds and effort. Mindful of oft-repeated ominous demographic trends [175] new approaches are needed. However, while no miracle cure is in the offing, we are not on an inevitable arc toward disaster. Perhaps the message that LOAD risk is potentially modifiable by multiple interventions has been lost in the pursuit of a universal remedy.

Alzheimer's disease research investigations are often harmonized with the amyloid cascade hypothesis. However, we may need to move past the widely accepted assumptions that Aβ species or their soluble/oligomeric/fibrillary forms are the only culprits underlying the pathogenesis of neurodegeneration and clinical manifestations of AD. A crucial first experimental step, capable of validating or refuting the amyloid hypothesis, will be to clearly establish the molecular forms of Aβ that are toxic to the brain and investigate their biophysical properties. Validation of this hypothesis may demand biopsies rather than experimental cell lines or animal models and will present a challenge due to the kaleidoscopic heterogeneity of Aβ. However, the ultimate validation of the amyloid cascade hypothesis will enable precisely targeted therapy which may produce significant results against dementia.

The route to dementia is varied and complex and we have simply equated EOAD and LOAD on the bases of their most striking neuropathological lesions [176]. Although the current mechanistic model is economical, exploring biochemical, biophysical and biomarker differences will lead to a better nosological understanding. Analogous to the situation in cancer research, the passage of time and accumulation of additional data may force an appreciation for the underlying biochemical heterogeneity of dementia and its implications [177-179].

New technologies embracing the use of human pluripotent stem cells and 3-dimensional human cell culture systems, which mimic the biochemistry and physiology of the human brain, may offer suitable models to better understand the dynamics of dementia than phylogenetically distant animal paradigms. The use of human brain biopsies [180] will be an indispensable approach that will provide information on the typical sequence of events preceding or precipitating the distinct classes of dementia. They will also afford appraisals of protein, lipid, carbohydrate and metabolite pools with state-of-the-art mass spectrometry and ultrasensitive immunoassays as well as ultramicroscopic assessments of structural cellular scaffolds, organelles and membrane pathology. The availability of biopsied brain tissue will also enable the discovery of uniquely time-dependent epigenetic changes and disturbed metabolic pathways involved in the pathogenesis and evolution of the different types of dementia. Furthermore, brain biopsies will also allow harvesting of autologous replacement cells that may restore cognitive function [181]. Neuroimaging advances will supply further information on specific quantitative imaging-detectable neuropathology such as Aβ, tau, α-synuclein, TDP-43 and other deviant molecular forms enabling improved selection and cohorting of patients for clinical trials. Neuroimaging innovations will also clarify the temporal sequence of neuronal and glial degeneration including myelin loss, defective connectivity configurations, synaptic density, brain microvascular disease, BBB status and detailed quantitation of chronic hypoperfusion and its functional consequences. In addition, improved computational models that integrate molecular network dynamics and data processing analysis will be pivotal in understanding the origin and dynamic evolution of the complex chain of inter-related events that lead to different forms of neurodegeneration.

Multiple lines of biochemical and clinical data confirm that LOAD is not inevitable and strongly suggest several important medical and behavioral risk factors are modifiable [182, 183]. The incidence of dementia may have stabilized or decreased in some high-income countries over three decades [184-185]. Although the exact causes behind these trends are unknown, they may reflect improved provision of medical services, enhanced educational levels and better control of cardiovascular diseases in addition to healthier diets and increased physical activity. Regrettably, a concurrent upsurge in obesity, diabetes and hypertension in the general population as well as the increases in life expectancy and population numbers may reverse these trends in the foreseeable future.

The Religious Order Study [156] and other investigations [186,187] reveal LOAD development risk may be recognizable early and imply the trajectory toward dementia could be altered through several intervention strategies. Late onset Alzheimer's disease emergence is clearly correlated with readily recognized and prevalent exacerbating medical issues such as diabetes [188, 189], mid-life hypertension [166, 190, 191] cardiovascular diseases [2, 166, 168, 192], depression [193-196] and anxiety [197] that are potentially subject to direct medicinal mitigation. In addition, practical behavioral interventions such as stress reduction strategies [198], regular exercise regimens [199-202], social engagement [203-206], intellectual attainment] [207-210], spirituality [211-215] and weight control [216-218] that are under the personal management of subjects may exert positive influences against dementia development risks. The vast unexplored and simultaneously underexploited territory of LOAD is the impact of the environment [219]. Nearly 25 years ago, Martin and Fukuchi [220] noted the complex interrelations between environmental factors and intrinsic aging processes that sometimes culminates in dementia.

It is clear that amyloid plays a pivotal role in the pathogenesis and pathophysiology of AD. The combined investment of research effort by academia and the pharmaceutical industry in search of an effective AD treatment has expanded understanding of dementia development and fundamental brain chemistry and physiology. Although there seem to be several pathways to dementia, it is important to recognize the contributions to healthy aging that active lifestyle interventions and education offer. Ultimately, as new imaging studies have confirmed, a substantial fraction of dementia cases may have etiologies distinct from what we presently designate as LOAD. Perhaps cancers sparked by an assortment of interacting genetic, epigenetic, physiologic and environmental factors, provide an apt analogy for dementia therapy. Vanquishing the multifactorial disorder, we know as Alzheimer's disease may oblige the implementation of several strategies because there are many ways to cross the Rubicon of dementia.

Acknowledgements

We express our gratitude to Dr. Vincent Marchesi, Dr. Walter Kalback and Ms. Chera Maarouf for critical review of the manuscript. The present study was supported in part by Midwestern University.

The authors declare no competing interests.

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