Biochimica et Biophysica Acta 1822 (2012) 340–349

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbadis

Dementia: Alzheimer pathology and vascular factors: From mutually exclusive to interaction☆

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ARTICLE INFO

Article history:
Received 18 May 2011
Received in revised form 30 June 2011
Accepted 6 July 2011
Available online 14 July 2011

Keywords:
Amyloid
Vascular
Dementia
Alzheimer's disease
Imaging

ABSTRACT

Alzheimer's disease (AD) is the most common type of dementia. Both its incidence and prevalence are expected to increase exponentially as populations' age worldwide. Despite impressive efforts of research worldwide, neither cure nor effective preventive strategy is available for this devastating disease. Currently there are several hypotheses on what causes AD, with the amyloid hypothesis being the most investigated and accepted hypothesis over the past 20 years. However the exact role of amyloid-β in the onset and progression of AD is not yet fully understood, and even the validity of the amyloid hypothesis itself is still being discussed. This debate is fuelled by the vascular hypothesis, as increasing epidemiological, neuroimaging, pathological, pharmacotherapeutic and clinical studies suggest that vascular pathology plays a key role in the onset and progression of AD. We here will discuss arguments in favor and limitations of both hypotheses within the framework of available literature, but also provide arguments for convergence of both hypotheses.
Finally we propose approaches that may aid in unraveling the etiology and treatment of AD. This article is part of a Special Issue entitled: Imaging Brain Aging and Neurodegenerative disease.

1. Introduction

Alzheimer's disease (AD) causes an immense economic burden and an unparalleled social challenge with over 15 million persons affected worldwide together with a decreasing number of potential caregivers in the coming decades [1]. Before Alzheimer's publication on the disease in 1907, dementia had been recognized for centuries and was ever since attributed to vascular factors as for example illustrated by Lobstein who coined the term "dementia arteriosclerotica", already as early as in 1833. And even before, the history of vascular dementia dates back to cases of dementia after apoplexia described by Thomas Willis in 1672.

In 1906, it was Alzheimer, or actually his teacher Kraepelin, who started confusion with the description of the case of 51-years old Auguste D that resembled "ordinary dementia" cases but who was considerably younger and had neuropsychiatric symptoms [2]. On post mortem neuropathological examination her brain contained senile plaques and neurofibrillary tangles.

This presenile disorder affecting patients in their forties and fifties with early symptoms of a severe progressive dementia with focal signs such as amnesia, aphasia, apraxia and agnosia was then named AD. In his later work, Alzheimer reported the degeneration of the smaller cerebral blood vessels at a cellular level in a 56 year-old patient, a process also referred to as Alzheimer's sclerosis. Alzheimer questioned whether the co-occurrence of plaques and tangles and vascular pathology being typical or atypical for AD, an ever actual issue.

After the identification of the plaque's main compound amyloid in the 1960's, much research was devoted on its physiology and pathophysiology, followed by a reappraisal of vascular factors based on the abundance of vascular changes in the brain of patients with cognitive decline and dementia when large scale neuroimaging became available [3–7].

Currently there are several hypotheses on what causes AD, with the amyloid hypothesis being the most investigated and accepted hypothesis over the past 20 years. However the exact role of amyloid-β in the onset and progression of AD is not yet fully understood, and even the validity of the amyloid hypothesis itself is still being discussed. This debate is fuelled by the vascular hypothesis,

Abbreviations: AD, Alzheimer's Disease; APP, Amyloid precursor protein; ApoE, Apolipoprtein E; CSF, Cerebrospinal fluid; DSM-IV, Diagnostic and statistical manual of mental disorders, 4th edition; DTI, Diffusion tensor imaging; MTA, Medial temporal lobe atrophy; PET, Positron emission tomography; PIB, Pittsburg Imaging Compound; WML, White matter lesions

☆ This article is part of a Special Issue entitled: Imaging Brain Aging and Neurodegenerative disease.

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doi:10.1016/j.bbadis.2011.07.003

as increasing epidemiological, neuroimaging, pathological, pharmacotherapeutic and clinical studies suggest that vascular pathology plays a key role in the onset and progression of AD. We will give a critical appraisal with respect to their causality in AD and provide a framework that enables a convergence of the two hypotheses towards one explanatory model for AD and that will provide clues for future research.

2. The amyloid hypothesis

2.1. Observational

The first description of the amyloid composition of the neuritic plaques, that Alzheimer observed decades before, appeared in 1966 by Roth, Tomlinson and Blessed. This British research group quantified the relation between clinical symptoms and pathological changes (plaques and tangles) in the brain [8,9]. In 1984 the amino-acid sequence of the amyloid-beta peptide was elucidated, that initiated the discussion on its origin [10]. The presence of the amyloid-β protein was first sequenced from (especially leptomeningeal) blood vessels of AD patients and patients with Down syndrome [11]. A year later the same peptide was recognized as the primary component of the senile (neuritic) plaques of AD patient brain tissue [12]. These findings resulted in the hypothesis that the blood borne accumulation of amyloid resulted in plaques. The subsequent cloning of the gene encoding for amyloid-β precursor protein (APP) and its localization on chromosome 21 and that of presenilin 1 and 2 that are now known to be involved in splicing the APP suggested that amyloid-β accumulation is the primary event in AD. Mutations in the APP gene were identified causing hereditary cerebral hemorrhage with amyloidosis (Dutch type), this showed that APP mutations could cause amyloid-β deposition, outside the brain parenchyma [13,14]. The amyloid-β protein is cleaved from APP by the sequential action of β-secretase and γ-secretase respectively; the resulting amyloid protein fragment can be either 40 ($A\beta_{1-40}$) or 42 ($A\beta_{1-42}$) amino acids in length. Mutations in the presenilins result in relative high levels of extracellular Aβ42 [15]. Many mutations in these genes have now been described, each with an early onset AD as clinical picture, but it should be noted that these mutations represent less than 0.1% of all AD cases [16].

Apoliporotein E (apoE) is the most consistently associated risk gene for AD, it is involved in the amyloid-β clearance and associated with increased amyloid burden and cholinergic dysfunction. Individuals with two apoE ε4 alleles have a more than seven times increased risk of developing AD [17].

In the late 1980s and early 90s it was recognized that amyloid-β protein was not only a pathological constituent but could also be part of physiological cellular mechanisms throughout life of healthy humans [18–20]. Based on these observations the later called "amyloid hypothesis" of AD was formulated (left panel, Fig. 1) [21,22]. In short, this theory implies that AD is initiated by abnormal cleavage of the APP resulting in a chronically enhanced production and/or decreased clearance of soluble, diffusible amyloid-β. This could lead to a gradual precipitation of aggregated non-diffusible amyloid-β in the form of spherical plaques and vascular deposits in AD. Factors which cause this aggregated amyloid-β include genetic causes like dominant mutations of the genes encoding APP and presenilin 1 and 2 [23,24].

In addition, tau, a microtubule-associated protein, is the major constituent of neurofibrillary tangles. The "amyloid hypothesis" proposes that an imbalance between amyloid-β production and amyloid-β clearance resulting in toxic concentrations of amyloid-β which triggers changes in tau and consequent neurofibrillary tangle formation [25], although the pathways linking amyloid-β and tau are not fully understood. Braak and Braak published the pathological stages of distribution of neurofibrillary tangles that followed a predictable pattern, with initial changes in the entorhinal cortex, than spread into the entorhinal region of the temporal cortex, followed by involvement of the neocortical associated areas [26].

There is still conflicting evidence between the amyloid burden and the attendant cognitive performance. In favor for a role of amyloid pathology in cognitive impairment was the observation that neurotoxic amyloid-β soluble oligomers could impair cognitive function in rats [27,28]. These highly organized, low molecular weight oligomeric assemblies precede the formation of amyloid fibrils and they have been identified in the brains of patients suffering from AD as well [29].

From the viewpoint that amyloid-β is a crucial factor in the etiology of AD it is evident that much effort has been put in its detection during life; ideally within the living brain or, second best, in

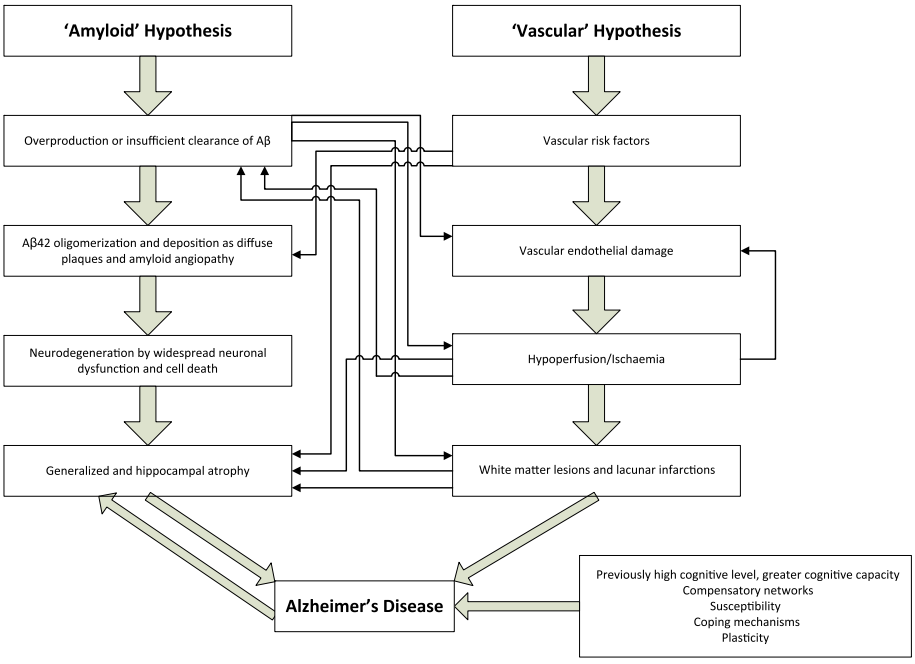

Fig. 1. Interaction between the amyloid hypothesis and the vascular hypothesis in the etiology of Alzheimer's Disease.

the cerebrospinal fluid (CSF). Indeed, recent research suggests that a fairly reliable distinction between AD and non-demented can be made on the basis of CSF findings [30]. However, the results seem less promising when other dementias, as in clinical practice, have to be distinguished, necessitating further research on the role of amyloid-β in the etiology, but also on its use as a diagnostic tool. Evidence from a longitudinal study suggests that CSF biomarkers, amyloid-β(1–42), tau and ptau-181, are not sensitive markers for disease progression in Alzheimer's patients [17]. Although others do not agree with this finding [31] and recent reports show a CSF AD profile in subjects with subjective and mild cognitive impairment [32] and a relation between increased levels of t-tau and intensity of disease and disease progression [33].

In-vivo detection of amyloid-β became possible with the development of the Pittsburg Imaging Compound B (PIB) and recently also other amyloid-probes that enable visualization of amyloid burden using Positron Emission Tomography (PET) scanning [34]. Positive cortical PiB binding has been associated with low cerebrospinal fluid Aβ42 concentrations in AD [35]. This development offers possibilities for early diagnosis and possibly also tracking progression of disease, although the latter could not be found in a recent small study, in which it appears that anti-amyloid therapies will need to induce a significant decrease in amyloid-β load in order to detect a drug effect with PIB PET [36]. As PiB is not ideal for commercialization, because of its 20-minute half life, several ^{18}F-labeled tracers have been developed [37]. At this time, these tracers are undergoing extensive phase II and III trials. Recently, it has been demonstrated that florbetapir-PET imaging was correlated with the presence and density of amyloid-β [38]. Next, to investigate the effect of novel amyloid-β modifying drugs on a clinical level, these amyloid binding agents may also have the potential to investigate the effects on the presence of amyloid-β in both the parenchyma as vessel wall.

2.2. Experimental

The ultimate proof for a role of amyloid-β peptide in AD would be to reduce the brain's amyloid-β burden, using disease modifying therapies and to investigate its effect on cognitive decline. As such the amyloid-β has become a major therapeutic target. Therapeutic strategies include lowering the production of the peptide by 1) prevention of APP transcription, 2) inhibiting the enzymes responsible for amyloid-β generation (APP splicing by β- and γ-secretase), 3) preventing aggregation of solid amyloid-β, and 4) increasing the rate of amyloid-β clearance from the brain. Amyloid-β immunotherapy uses anti amyloid-β antibodies, generated following vaccination or introduced passively. Preclinical studies in animal models showed that amyloid-β immunization lowered the plaque burden [39] and reversed behavioral deficits [40]. First phase human clinical trials in AD in which patients were immunized with aggregated human amyloid-β 1–42 to stimulate clearance of amyloid plaques were associated with serious adverse events (meningoencephalitis), the trial had to be terminated prematurely [41]. Later analysis of this interrupted trial showed that some patients ("the antibody responders") had an increased loss of brain volume and no better cognitive performance compared to the placebo group, except for some composite z-score of the neuropsychological test battery [41,42]. On the basis of these studies numerous amyloid-β immunotherapies are currently in human clinical trials.

Another approach to decrease levels of amyloid-β is passive immunization with antibodies targeting portions of the amyloid-β molecule. Bapineuzumab is a humanized monoclonal antibody investigated in two trials. In the first trial the amyloid-β burden was decreased, however in the other trial no difference was found in cognitive function between the treatment group and the controls [43,44]. A safety concern was the occurrence of reversible vasogenic edema.

Another area of drug development involves the targeting of γ secretase, one of the enzymes required for production of amyloid-β from APP. As γ-secretase has many functions in the body, treatment with γ-secretase inhibitors may lead to toxicity. Nevertheless a number of inhibitors have been tested. Recently, a large, multicentre, randomized, double blind, placebo-controlled, phase III trial on Tarenflurbil showed no beneficial effect in the treatment group compared to placebo [45].

In addition, although several observational studies have concluded that the use of nonselective nonsteroidal anti-imflammatory drugs (NSAIDs) is associated with a reduce risk of AD, [46] clinical trials of nonselective or COX2-selective NSAIDs in patients with dementia or with mild cognitive impairment have not demonstrated any effect on cognitive performance [47–49].

Possible explanations for these negative trials may be because of their use in patients with advanced stages of disease, the pathological processes may start years before the onset of clinical symptoms, this suggests that treatment administration would need to occur much earlier in patients deemed to be at high risk. In addition, it might be because of study design, sample size or choice of treatment dosage. However, it may also be that the negative findings reflect the still incomplete understanding of the pathogenesis of AD, and the role other (neurodegenerative and vascular) factors.

2.3. Discrepancies

Notwithstanding the overwhelming observational data on amyloid and AD, some important issues need to be addressed.

First discrepancy is the negative results of the trials in which the effect of amyloid-β lowering drugs on disease was studied. In addition, pathological studies on the relation between senile plaques and neurofibrillary tangles (AD pathology) and cognitive performance and clinical AD show various discrepancies. There are numerous reports showing a lack between the degree of amyloid pathology and cognitive function during life [50], whereas other studies correlated soluble and fibrillar forms of amyloid-β with cognitive scores [51,52]. Many cognitively intact, healthy elderly have abundant senile plaques, some even with the same density of senile plaques as patients with AD in their brains without clinical signs of AD [53,54]. Plaques and tangles are found in cognitive intact individuals after the age of forty without neuronal loss [55]. This is in line with findings from a large pathology study that found that there is much mixed pathology (cerebrovascular and AD pathology) in healthy individuals from the general population who did not meet the clinical diagnostic criterium of dementia [56]. There are reports on several lines of transgenic mice over expressing APP in which there is a correlation between the extent of learning and memory deficits and the amount of deposited amyloid-β found in the central nervous system, [57] however there are also reports on transgenic animal models with high levels of brain amyloid deposits that show no significant neurodegeneration [58]. A recent report shows that neuropathological processes related to AD in persons without dementia were correlated with subtle cognitive dysfunction and that by the age of 80–85 years many non-demented elderly have substantial AD pathology [59]. Furthermore, recent studies in humans showed that clearance of amyloid depositions resulted neither in cognitive improvement nor in a decreased rate of mental deterioration. These observations suggests that senile plaques may not be the main cause of neurodegeneration and cognitive decline in AD, accordingly other theories have been established over the past years.

The first theory is based on soluble amyloid-β, which proposes that toxic amyloid-β-42 or its oligomers interfere with synaptic plasticity in vitro of with membrane dysfunction and promote cell death [60,61]. However these findings are based on experimental animal's models, over expressing exogenous APP, and may not be applicable to AD. Soluble amyloid-β peptides however are normal components of

human serum and cerebrospinal fluid and it is not clear under what conditions these peptides become toxic, especially as no significant disease-associated abnormalities have been detected with their production [62].

The second theory is the presenilin hypothesis which suggests that loss of function of presenilin may be the primary event triggering neurodegeneration in AD. Amyloid-β-42 may act primarily to antagonize presenilin dependent functions, possibly by operating as active site-directed inhibitor of γ-secretase, mimicking the effect of presenilin mutations. Loss of presenilin activity results in synaptic dysfunction and ultimately leads to progressive neurodegeneration characterized by loss of synapses, dendrites, and neurons, astrogliosis and tau hyperphosphorylation [63].

Finally, others suggest that tau protein plays a central role in the chain of events leading from amyloid neurotoxicity to tau hyperphosphorylation, microtubular destabilization, disturbed axonal transport and synaptic failure to neurodegeneration. In this hypothesis the pathological conversion of normal tau into functionally impaired phosphorylated tau, which forms neurofibrillary tangles and dystrophic tau neuritis and thereby depleting levels of functional microtubules binding and stabilization tau below a critical point that results in depolymerization of microtubules and a disruption of axonal transport. These events are thought to culminate in neuronal dysfunction and degeneration, leading to AD [64].

Other mechanisms may also play a role, for example the cognitive reserve theory [65]. The cognitive reserve theory provides at least two explanations of not finding a relation between the degree of amyloid pathology and cognition. The first is that individuals functioning at a previously high level possibly have a greater cognitive capacity and/or more efficiency and in that way may be less susceptible to disruption compared to the average elderly. Consequently, they may experience a longer subclinical cognitive deterioration, despite the possible presence of amyloid plaques. Another explanation could be the presence of compensatory networks that may compensate for amyloid-based disruption of pre-existing networks [26]. This may obscure the relation between amyloid burden and the cognitive decline during the course of AD.

3. Vascular hypothesis

3.1. Observational

The history of vascular dementia can be traced back to cases of dementia postapoplexia described by Thomas Willis in 1672. In 1833 Lobstein introduced the term “dementia atherosclerotica”. In 1894 Binswanger described the subcortical arteriosclerotic encephalopathy, now known as Binswanger disease. Before the CT and MRI era this disease was thought to be very rare.

With the advent of non-invasive imaging of the brain with CT in the 1970s and 1980s and MRI in the 90s it became evident that small vessel disease was not rare at all and a common finding in the general population and in AD patients. The term “leuko-araiosis” was introduced only 25 years ago as a neutral term for deep white matter changes on the basis of vascular disease that were considered to be associated with cognitive impairment [66]. It was demonstrated that “healthy” elderly with leuko-araiosis performed less on certain cognitive tasks than those without leuko-araiosis and that, in patients with AD, leuko-araiosis was associated with a greater degree of cognitive impairment [67,68]. Large longitudinal population based cohort studies were then initiated and consistently showed a relation between several vascular risk factors and white matter lesions (WML) [69–71]. These vascular risk factors, hypertension, diabetes, atherosclerosis, homocysteine, smoking and atrial fibrillation have found to be related to AD [72–76]. Presumably these relations underlie the emergence of vascular (white matter) lesions, as it was demonstrated that individuals with silent brain infracts, periventricular and subcortical WML have an increased risk of AD [4]. Furthermore, pathology studies have revealed the presence of ischemic lesions in patients with AD and it was shown that among non-demented people those with coronary heart disease had greater plaque burden in the brain those without heart disease [77]. This resulted in large population based autopsy studies to unravel the vascular risk factors for cognitive decline in elderly. In a prospective population based cohort study, 209 subjects consented to donate their brain for post-mortem evaluation. Before, they all underwent neuropsychological screening with incident dementia at 2 and 6 years as the primary outcome measure [56]. The median age of death was 85 years; at that time 48% of the subjects were demented of which 64% fulfilled the criteria for probable or definite AD. Over one third of the clinically diagnosed AD patients did not have any plaques at all whereas in one third of the clinically non-demented elderly moderate to severe plaques were found. Around 80% of the subjects had vascular abnormalities of the brain, which were significantly more severe in the demented population. The vascular hypothesis emanated from these findings (Fig. 1, right panel). Vascular risk factors induce neurovascular dysfunction and cause endothelial damage by oxidative stress and inflammation which lead to local hypoperfusion and ischemia which are radiologically represented by WML and silent and/or lacunar brain infarctions [78]. As discussed earlier, these radiological changes are related to cognitive decline and dementia [4].

3.2. Experimental

Proof of concept for a role of vascular factors in the etiology of dementia could come from intervention trials. In the Syst-Eur trial showed that treatment of isolated systolic hypertension with calcium antagonists among elderly over the age of 60 was associated with a decrease of incident dementia. The absolute risk reduction was 3% [79]. A 2-year open label extension of this study revealed the same results; long-term antihypertensive therapy reduced the risk of dementia by 55% compared with placebo ($p<0.001$) [80]. In the Leiden 85-plus study it was also reported that the use of a calcium antagonists prevents the development of dementia, they did not find this for other antihypertensive drugs. They suggested that the protective effect found in the Syst-Eur trial and in their own study was due to the effect of the calcium channel inhibition rather than its blood pressure lowering properties [81]. The PROGRESS study was a randomized, double blind, placebo controlled trial involving 6105 patients with previous stroke or ischemic attack. Participants were assigned to active treatment (perindopril for all participants and indapamine for those with neither an indication for nor a contraindication to a diuretic) or matching placebo(s). After a follow-up of 3.9 years the risk of dementia was reduced from 7.1% to 6.3% (nonsignificant) however the risk of cognitive decline was significantly reduced from 11% to 9.1%. Although, it could be that this benefit was due to the prevention of recurrent stroke [82]. Preliminary results of the observational OSCAR study support these findings [83].

3.3. Discrepancies

The previously described intervention studies could not be replicated in several other studies. In the SHEP (systolic hypertension in elderly program) study over 2000 patients were enrolled for treatment with chlortalidone or placebo. Neither the decline in cognitive function nor the incidence of dementia was significantly different between both groups after the treatment period [84]. In the PROSPER study 6000 individuals with pre-existing vascular disease or raised risk of such disease were randomized to either pravastatin or placebo and followed for a mean of 3.2 years; one of the secondary outcomes was cognitive decline. There were no significant differences for both groups and several cognitive rating scales [85].

A Cochrane review with a meta-analysis of four randomized controlled trials (Syst-Eur trial, Scope trial, SHEP trial and the HYVET trial) [79,84,86,87] on the effects of blood pressure lowering in late-life on the development of cognitive decline and dementia on patients with hypertension without apparent prior cerebrovascular disease. This Cochrane concluded that blood pressure lowering in late-life is not indicated with the aim of prevention of cognitive decline or dementia alone, as only the Syst-Eur trial reported a benefit from treatment but neither the SCOPE, SHEP nor HYVET showed a benefit, and when the trials were entered in a meta-analysis, no statistically significant effect was seen [88]. As suggested by the authors, primary outcome measures of all trials was cardiovascular disease, cognitive function and dementia were secondary end-points. Trials were terminated once the primary end-points were shown, in that way possible beneficial effects on cognition later in the follow-up can be missed.

One of the possible explanations for this unequivocal role of (treatment of) hypertension could be that the deleterious effects of vascular risk factors in general and hypertension specific already occurs decades before either cardiovascular or cognitive symptoms occur. By the time the risk factors result into disease, the damage is not remediable anymore.

4. Convergence of the amyloid hypothesis toward the vascular hypothesis

The diagnosis AD is based on the DSM-IV-TR [89] and the NINCDS-ADRDA criteria [90]. In these criteria, the presence of other systemic or brain diseases that may account for the progressive memory loss and other cognitive deficits, is an exclusion criterion. The criteria for vascular dementia (NINDS-AIREN) include decline from a previously higher level of functioning and manifested by impairment of memory and of two or more other cognitive domains, which also exclude patients systemic or brain disorders (such as AD) that in themselves could account for deficits in memory and cognition [91]. According to these criteria the presence of cerebrovascular disease in a demented individual rules out AD and vice versa.

However, the pathological change characteristics of AD are observed together with vascular pathology in more than 40% of elderly demented individuals [92]. Several studies show a variety of underlying neuropathology among clinically diagnosed “probable” AD patients. This pathology includes both Braak and Braaks' criteria fulfilling amyloid plaques and tau tangles but also vascular lesions such as lacunar infarctions and WML. A study among 102 women between 76 and 100 years showed that dementia prevalence was highest among those who met the neuropathological criteria for AD and had coexisting vascular pathology [93]. In the presence of vascular pathology in the basal ganglia, thalamus and deep white matter fewer neuropathologic lesions were needed to result in a clinical diagnosis of AD than in those without coexisting vascular pathology, indicating the possible interaction between these factors. In contrast, among those who did not meet the neuropathological criteria for AD, vascular lesions were only weakly associated with poor cognitive function and dementia. The Honolulu Asia Aging Study, a community based study in very old men, of which 29% were demented ante mortem, suggested that the burden of AD and vascular lesions independently contribute to a clinical AD diagnosis, which is compatible with the view of the additive effect that these two types of lesions on cognitive impairment may have [94]. The combination/interaction of cerebrovascular damage with damage to the brain caused by amyloid-β may result in a lower cognitive threshold of dementia than the two separately [93]. The simultaneous double hit by amyloid-β and vascular damage might affect cognitive function more than the sum of parts, their effects may even be synergistic [95,96].

These findings are more or less confirmed by the MRC CFAS study that showed an extensive overlap of intermediate Alzheimer type pathology among demented and non-demented older people despite equivalent degrees of vascular pathology [56].

In addition, hypoxia and ischemia resulting from vascular insufficiency may interact with amyloid-β on a more basic pathofysiological level. They increase the transcription of APP and its cleavage by β-secretase resulting in more amyloid-β production [97,98]. Furthermore vascular damage may promote amyloid-β accumulation in the CSF by reducing the vascular clearance of this peptide [99,100]. And vascular amyloid-β is a potent vasocontrictor and impairs fundamental mechanisms regulating cerebral circulation and in that way may induce ischemia [101,102]. In that way the interaction between the amyloid and vascular pathway enhances their pathogenic effects and favor the formation of amyloid plaques and cerebral amyloid angiopathy (CAA) [103]. Others Imaging of in vivo parenchymal and vascular amyloid-β, with PET-radiopharmaceuticals could help in studying these potential self strengthening mechanisms [104]. Next to investigate the effect of novel amyloid-β modifying drugs on a clinical level, PIB-PET may also have the potential to investigate these effects on the presence of amyloid-β.

Neuroimaging studies lend further support for an interaction between amyloid-β features with vascular factors and vice versa. The key radiological hallmark of typical AD is the medial temporal lobe atrophy (MTA). The degree of atrophy was reported to be related to the disease stage defined by Braak and Braak [105,106] but a relation between vascular (risk) factors and the severity of MTA has also been observed [107,108]. Non-demented patients with diabetes have more MTA on MRI than those without diabetes [109]. At the population level there is a positive association between blood pressure and medial temporal lobe atrophy meaning that increase in blood pressure was related to more severe MTA [110]. Among patients with AD a linear relation between systolic blood pressure and the severity of MTA has been observed. WML could be a possible intermediate in this relation as both population based studies and studies among AD patients showed a relation between WML and MTA [107,108]. A small prospective study showed that baseline WML was associated with progression of MTA among 35 clinically defined “probable” AD patients. Stratification on WML indeed revealed that the relation between blood pressure and MTA only existed in AD patients with WML [111]. In stroke patients it was shown that patients with post-stroke reduced episodic memory function had reduced medial temporal lobe functionality as demonstrated by fMRI [112]. Other cardiovascular risk factors than hypertension have been related to AD. Diabetes mellitus doubles the risk of AD corresponding with an increase in microinfarcts and without a corresponding increase in plaques and tangles [113]. Higher total cholesterol, LDL concentrations and a history of diabetes is associated with faster cognitive decline in AD [114]. Additionally, in studies on AD patients the presence of atherosclerosis was related to an increased frequency of neuritic plaques and neurofibrillary tangles [115,116]. Furthermore, treatment of vascular risk factors in patients with AD is associated with slower cognitive decline [117]. Conversely, there is increasing evidence for a role of the amyloid metabolism on presumed cerebral vascular lesions and its effects on cerebral blood vessels. Cerebral microbleeds might be a missing link between the amyloid and vascular hypothesis. Cerebral microbleeds in the cortico-subcortical regions might be a marker of CAA [118]. CAA is characterized by of deposition of amyloid-β peptide within the walls of the small and medium sized cerebral arteries [119], and is associated with AD [120]. ApoE plays a crucial role in lipid metabolism and neuronal repair [121]. The apoE ε4 allele is not only associated with cognitive impairment and dementia, but also with vascular risk factors for WML [122]. ε4 homozygotes exhibit more extensive WML than other genotypes [123]. It was hypothesized that the ε4 allele was related to cognitive impairment because of the presence of WML.

Large population based studies showed interactions between hypertension and apoE ε4 allele with regard to subcortical WML, and relations between plasma amyloid-β levels and WML and lacunar infarcts in people who carry an apoE ε4 allele [124,125]. However, studies in demented populations and other population based studies could not find these relations [126,127]. The ε4 allele modulates the severity of amyloid-β deposits in animal models [128] and in humans [129], especially in patients with WML [130]. In a sample of autopsy proven of AD patients apoE ε4 was associated with small vessel arteriosclerosis, microinfarcts, neuritic senile plaque density and CAA [131]. On the other hand cerebral microbleeds in the deep gray matter and infratentorial regions are related to hypertensive vasculopathy and might be a result of microangiopathy, such as arteriosclerosis or ischemia [132].

In addition, experimental findings suggest cytotoxic effects of amyloid-β on the vascular smooth muscle cells, resulting in prolonged and intensified endothelium dependent vasoconstriction that could possibly result in hypoperfusion [101]. In a study, based within the same Rotterdam Study, in-vivo support for these observations has been obtained. High plasma levels of amyloid-β assessed 6.5 years before transcranial Doppler investigations were related to impaired CO2 enhanced transcranial Doppler assessed vasomotor reactivity [133].

Next to this classical approach, novel developments, including those from other areas, may help in elucidating the cause of AD. One of these could be the systems approach to the networks of aging as proposed by West [134]. This approach emphasizes the multiplicative effect that damage in network systems such as the vascular tree may have on organ functions in general. In this way the cerebrovascular damage, probably highly related to amyloid plaque depositions in the vascular wall, may act in a synergistic way with the amyloid plaques, leading a further compromised neuronal function. In addition this theory makes use of the fundamental physiological properties of different species as they age with molecular and cellular changes, analyzing a system from both a top-down (a system decomposing into parts), but also from a bottom-up approach.

5. Future perspectives

Most likely there is no single one-risk factor based explanatory model for AD as more and more evidence suggests that it is not a single cause disease entity, but a variety of causes, including neurodegenerative (amyloid-β), vascular and probably more.

None of these risk factors alone is proven to be a necessary risk factor (which means that the disease (AD) must always be preceded by this risk factor) or sufficient risk factor (i.e. the risk factor always leads to the disease). Most likely the factors described here are contributory risk factors (the risk factor is sometimes succeeded by AD and the other way around). In addition to this interaction between several of these factors may also play a role in the final development of the clinical syndrome of AD as we call it today (Fig. 1).

Dementia is very complex disease in the elderly with a large heterogeneity in phenotype and genotype, with a heterogeneous lifetime exposure to a lot of different frequently interacting vascular, amyloid and/or other damaging risk factors.

In future research more distinctive and reliable biomarkers might play an important role, yet they are part of the revised research criteria for AD, proposed to allow earlier and more specific AD diagnosis [135].

Although some discrepancies as discussed earlier, CSF markers may be a potentially promising approach for pathology in vivo, as they can distinguish between AD and non-demented patients and it was shown that subjects with subjective and mild cognitive impairment have a AD CSF profile, and this profile was predictive of AD-type dementia[30,32] are related to. If amyloid deposition plays an important role in the etiology of AD, development of anti-amyloid-β therapies, including amyloid-β immunotherapy, that reduce the plaque burden or even prevent the development of amyloid plaques is one of many future approaches to reduce the ever-growing incidence of AD.

Imaging can be used as another biomarker. With the advance of imaging techniques that are now available, repeated imaging with thinner slices in combination with a valid automated lesion detection tool could quantify the total lesion volume more precisely. Furthermore, as identical appearing WML on conventional MRI are actually histopathologically heterogeneous, [136] it could be that only WML with the highest loss of structural integrity are related to cognitive impairment. It is also important that only a small portion of the white matter (usually less than a few percent) is affected by WML. As conventional MRI is not sensitive to early loss of microstructural integrity in the normal appearing white matter, possible changes in this largest part of the white matter cannot be assessed. The integrity of the normal appearing white matter might be an important factor for a better understanding of the relation between white matter integrity and cognitive function and decline. These limitations of conventional MRI can potentially be overcome with the use of novel imaging techniques as Diffusion Tensor Imaging (DTI) which allows the assessment of the microstructural integrity of the whole white matter [137]. DTI may particularly be suited to detect subtle white matters' structural abnormalities at even earlier moments in time (at least before detection with conventional FLAIR imaging). And as such these early signs of microstructural loss can be found before actual disabling cognitive consequences may have occurred and as such may aid in the selection of patients who may be at risk for future development of "leuko-araiosis" and the possible attendant cognitive decline. Even more stringent treatment of vascular risk factors may, although unproven until now, possibly postpone future cognitive deterioration. In future it could be possible to use these new imaging techniques to visualize neural compensation networks. Therapeutic strategies may then be developed that aim at stimulating the formation of such networks.

Analogous to the amyloid theory much needs to be done to establish a causal role for vascular factors in the etiology of dementia, as most of the data are cross-sectional or of non-replicated intervention studies. In future research on the etiology of AD and the possible role vascular factors in this etiology, the phenotype of the study population should critically be defined. This phenotype should be defined by the clinical presentation, exposure to risk factors and age of the study population. In etiologic research, the phenotype should not be based on the absence or presence of biomarkers as these are the etiologic factors you want to investigate and when part of the diagnosis, obviously there will be a relation between the biomarker and disease. It should be a very large study sample in order to be able to define subgroups to investigate interactions between these groups. In prognostic or intervention trials biomarkers can be used in the definition of disease, although there should be consensus on the definition of these biomarkers. For example, the presence of WML, there can rated semi-quantitatively, by location, by volume estimation or by automated or manually segmented total volume, and with or without taking silent brain infarcts or lacunar infarcts into consideration or by using new imaging techniques which assess the microstructural integrity of the whole white matter. Dementia should be among the endpoints in any cardiovascular intervention trial, with an extended, open-label follow up to be able to detect incident dementia occurrence after the primary vascular outcome events.

6. Conclusion

In 1907, Aloïs Alzheimer described a clinical syndrome, now known as AD, characterized by progressive behavioral abnormalities with prominent focal symptoms and an impaired memory in a relatively young woman.

Nowadays, patients that are being diagnosed with AD are usually much older than Auguste D and the clinical symptoms differ. Alzheimer most likely described a presenile dementia based on amyloid-β pathology without, or with only few concomitant (vascular) risk factors. Although some clinical similarities between Auguste D's dementia and the senile dementia exist, the latter is probably being caused by accumulated cerebral damage caused by life-time exposure to vascular, amyloid and/or damaging factors that probably differs in terms of pathophysiology from Auguste D.

Vascular factors as a contributing cause to the development of AD have come into play again, next to affecting the large arteries at the skull's base as one thought in the 19th century, the small vessels (arterioles) deep within the brain parenchyma also play a role. The presence of small vessel cerebrovascular disease in AD is very common; cerebrovascular disease and AD share the same risk factors, coexisting cerebrovascular disease and AD results in more severe cognitive impairment, either by direct damage of the neural pathway or indirect by worsening the impact of AD pathology.

As hypothesized by others, this suggests that cerebrovascular disease may be in the causal pathway for development of AD or interacts synergistically with AD pathology [103,138].

Future studies on the etiology of AD should preferably start with proper diagnostic research criteria in order to exactly define the disease investigated instead of etiologic research on merely a complex of symptoms rather than a single disease entity. A well described phenotype and large numbers of patients are important factors to enable unraveling the complex interacting pathologies, best in etiological studies in vivo using MRI, CSF markers and PET [135]. Once that has been accomplished studies on etiology should be large, prospective and presumably already start during mid-life or even before. Treatment of risk factors found by this approach should then be further evaluated in intervention studies with dementia as a primary end point. We should also keep an open eye towards innovative approaches including those derived from systems biology, a field which focuses on complex interactions of biological systems, [134] that may possibly speed up the quest for the etiology of AD.

Imaging and biomarkers have improved dramatically over the last ten years. Identifying the individuals at risk before clinical onset of symptoms, might help us the treat these individuals and to reduce the ever growing incidence of AD.

Acknowledgements

F.E.d.L. and E.J.v.D.: received personal fellowships of the Dutch Brain foundation (H04-12; F2009(1)-16); F.E.d.L. clinical fellowship of the Netherlands Organization for Scientific Research (project number: 40-00703-97-07197). This study was supported by the 'Internationale Stichting Alzheimer Onderzoek' (number 8510).

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