

Risk factors for Alzheimer's disease

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Abstract

Early reviews identified over 20 risk factors associated with Alzheimer's disease (AD) including age, familial inheritance, exposure to aluminium, traumatic brain injury (TBI), and associated co-morbidities such as vascular disease and infection. In the light of recent evidence, this review reconsiders these risk factors, identifies those currently regarded as important, and discusses various hypotheses to explain how they may cause AD. Rare forms of early-onset familial AD (EO-FAD) are strongly linked to causal gene mutations, viz. mutations in amyloid precursor protein (APP) and presenilin (PSEN1/2) genes. By contrast, late-onset sporadic AD (LO-SAD) is a multifactorial disorder in which age-related changes, genetic risk factors, such as allelic variation in apolipoprotein E (Apo E) and many other genes, vascular disease, TBI and risk factors associated with diet, the immune system, mitochondrial function, metal exposure, and infection are all implicated. These risk factors may act collectively to cause AD pathology: 1) by promoting the liberation of oxygen free radicals with age, 2) via environmental stress acting on regulatory genes early and later in life ('dual hit' hypothesis), or 3) by increasing the cumulative 'allostatic load' on the body over a lifetime. As a consequence, life-style changes which reduce the impact of these factors may be necessary to lower the risk of AD.

Key words: Alzheimer's disease (AD), risk factors, aging, genetics, environmental factors, allostatic load.

Introduction

Early reviews [74,76,79,80,109], and especially that of Henderson [76], identified many of the risk factors associated with dementia in general and Alzheimer's disease (AD) in particular. Over 20 different risk factors associated with AD were discussed by Henderson [76] and a common pathogenesis proposed as to how they might cause the pathological changes characteristic of AD, viz. β -amyloid (A β) immunoreactive senile plaques (SP) [57] and tau immunoreactive neurofibrillary tangles (NFT) [59]. More recent research suggests that of the factors discussed by Henderson [76], support for some has increased, others reduced, while new risk factors

have also been identified. Hence, in a recent review, over 60 environmental risk factors alone were identified associated with AD and classified into six categories, viz. air quality, heavy metals, other metals, trace elements, occupational exposure, and miscellaneous [101]. It remains a major challenge to explain how many apparently disparate risk factors could contribute to AD.

Historically, the term AD was first used in 1910 by Kraepelin based on the clinical and pathological description of Alzheimer's original cases [8]. Of the two cases originally described by Alzheimer, however, both had numerous SP, but only one had significant numbers of NFT [63], thus identifying the pathological heterogeneity characteristic of AD [14],

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and creating difficulties in establishing a single theory as to its cause [10]. Originally the term AD was applied to early-onset cases only which were regarded as distinct from the more common late-onset cases referred to as 'senile dementia' [76]. It was the discovery of molecular markers associated with AD pathology, viz., A β [57] and tau [59], that suggested that pre-senile and senile dementia were essentially subtypes of the same disease. Subsequently, the 'amyloid cascade hypothesis' (ACH) was proposed as a general model of the molecular pathology of AD [72] (Fig. 1). The hypothesis was initially based on the study of early-onset familial AD (EO-FAD) linked to mutations of the amyloid precursor protein (*APP*) gene and later extended to other genes such as presenilin 1/2 (*PSEN1/2*), and then to all forms of AD. This hypothesis suggested the deposition of A β in the form of SP was the initial pathological event in the disease leading to the formation of NFT, cell death, and ultimately dementia. As a consequence, the significance of a risk factor for AD is often assessed by the degree to which it influences APP metabolism. Nevertheless, the significance of the ACH as a general model of AD has been questioned [11] and a recent review also identified nine modifiable risk factors for the disease which appeared to act independently of A β and tau pathology [117].

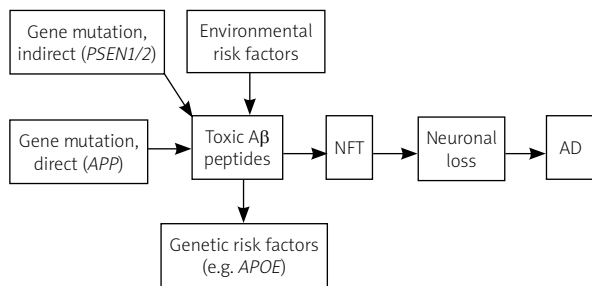


Fig. 1. The 'amyloid cascade hypothesis' (ACH) [72] as a general model of the pathogenesis of Alzheimer's disease (AD). In this scheme the amyloid precursor protein (*APP*) gene acts directly, the presenilin (*PSEN1/2*) genes more indirectly, and together with genetic risk factors such as the apolipoprotein E (*APOE*) gene and environmental factors, all act to increase the production of toxic β -amyloid (A β) peptides leading to neurofibrillary tangles (NFT), neuronal loss, and ultimately dementia.

Subsequently, many theories have been proposed to explain AD, especially the late-onset sporadic form of the disease (LO-SAD), including exacerbation of aging, genetic factors, exposure to aluminium, head injury, diet, mitochondrial dysfunction, vascular disease, immune system dysfunction, and infectious disease [10]. However, no single theory has gained universal acceptance and it has become increasingly recognised that multiple risk factors are likely to be involved. Given recent advances, it would appear timely to update earlier reviews, to reconsider the current state of knowledge regarding the risk factors for AD, and to address two questions: 1) to what extent does existing knowledge identify credible risk factors for AD and 2) how can this information be integrated into a hypothesis to explain the pathogenesis of AD? The major risk factors currently considered to be associated with AD are summarised in Table I.

Risk factors

Age

Many epidemiological studies, including those quoted by Henderson [76], agree that of the various demographic factors such as age, gender, race and social class, age is one of the most important risk factors for cognitive decline [43] and AD [78]. With advancing age, the prevalence of AD increases to an estimated 19% in individuals 75-84 years of age [103] and to 30-35%, possibly up to 50% for those older than 85 years [48]. That AD could therefore be an accelerated form of normal aging is largely based on the observation that many of the pathological changes identified in AD are similar, apart from their severity, to those present in normal aging [154,160]. Hence, in cognitively normal brain, there is an age-related reduction in brain volume and weight, enlargement of ventricles, and loss of synapses and dendrites in selected areas accompanied by SP and NFT [87]. Hence, a cross-sectional study by Miller *et al.* [134] investigated changes in density of SP and NFT with age in 199 individuals and observed from age 71, an abrupt increase in the numbers of both lesions. In addition, in 60 normal elderly cases, 32/60 had no SP, although 30/60 were younger than 65 years, 13/60 had SP in the HC, and 12/60 had SP in temporal cortex [121]. It was concluded that it was not possible to distinguish early AD from normal aging at post-mortem [121]. Moreover, in the

Table I. A summary of risk factors that have been associated with Alzheimer's disease (AD)

Grouping	Risk factor
Demographic	Age [43,78,76]
	Education [76,92]
	Gender [76]
	Race [76]
	Social class [76]
Genetics	Amyloid precursor protein (<i>APP</i>) [39,58]*
	Presenilin 1 and 2 (<i>PSEN1/2</i>) [112,170]*
	Apolipoprotein E (<i>APOE</i>) [110,166,181]
	ATP-binding cassette transporter A1 (<i>ABCA1</i>) [105]
	Adaptor protein evolutionarily conserved signalling intermediate in Toll pathway (<i>ECSIT</i>) [175]
	Clusterin gene (<i>CLU</i>) [150]
	Estrogen receptor gene (<i>ESR</i>) [162]
	Fermitin family homolog 2 gene (<i>FERMT2</i>) [38]
	Glyceraldehyde-3-phosphate dehydrogenase (<i>GAPDH</i>) [5]
	Histocompatibility locus antigen (HLA class III) [40,77,190]
	mtDNA haplotype [165]
	Transferrin gene (<i>Tf</i>) [194]
	Triggering receptor expressed on myeloid cells 2 (<i>TREM 2</i>) [161]
	Vascular protein sorting-10 domain (<i>VPS10</i>) genes [108]
	Vitamin D receptor gene (<i>VDR</i>) [193]
	Epigenetic factors [106,107]
	Lifestyle
Lack of exercise [76,102,152]	
Lack of cognitive activity [92,174]	
	Malnutrition [1,76,189]
	Poor diet [65,167,168,176,196]
	Smoking [37,76,173]
Medical	Cancer [173]
	Cardiovascular disease [76,95,116]
	Congestive heart failure [76,81]
	Immune system dysfunction [12,128,141,158]
	Micro-infarcts [27]
	Obesity [31,71,125,185]
	Poor cholesterol homeostasis [110]
Poorly controlled type-2 diabetes [4,118,124]	
Stroke [203]	
	Traumatic brain injury (TBI) [53,76,80,93,129,130,131,139,169]
Psychiatric	Depression [50,21]
	Early stress [82,148]
Environmental	Air pollution [101]
	Calcium deficiency [76]
	Geographic location [76]
	Metals (especially aluminium, copper, zinc) [16,86,147,156]
	Military service [60]
	Organic solvents [76]
	Occupation [101,147]
	Vitamin deficiency [68,126,139]
Infection	Bacteria, e.g. <i>Chlamydomphila pneumonia</i> , <i>Treponema</i> [19,55,133]
	Dental infections [159]
	Fungi [7]
	Viruses [114,164,197]

*regarded as causal factors

study of Bergeron *et al.* [28], SP were observed in 60% of normal elderly cases, albeit at lower density than in AD. Similarly, Arriagada *et al.* [15] reported SP in most normal individuals older than 55 years of age suggesting a 'continuum' of pathological change from elderly non-demented brains to early AD, and then to advanced AD [9]. In addition, the density of SP with a distinct 'core' ('classic' plaques), were not significantly different in AD and aging [26].

Whether NFT occur in the normal aging brain is more controversial. Some studies suggest that the majority of cognitively normal individuals have low densities of NFT [104] with Braak stages 1/2 being

characteristic of cognitively normal individuals and higher stages of at least mild cognitive impairment (MCI), and there is also less astrocytosis and microglial reaction [41]. By contrast, Bouras *et al.* [32] found that all non-demented cases had NFT in layer II of the entorhinal cortex and in sector CA1 of the HC. Moreover, in non-demented individuals, NFT were more numerous in medial temporal lobe (MTL) regions and in cortical association areas when a memory deficit was present suggesting NFT could be related to memory loss in non-demented individuals [70]. In the MTL, the perforant path appears to be especially sensitive to the development of NFT in AD and these changes

may be distinct from those seen in normal aging even in the oldest individuals [52].

Two further age-related pathological processes may be involved in AD. First, breakdown of myelin and therefore, of white matter fibre tracts [24], although some studies suggest that myelin loss occurs late in the disease secondary to neuronal degeneration [33]. Second, loss of cells occurs in brain stem nuclei such as the locus coeruleus (LC), which provides an input of noradrenaline to the cortex via terminal varicosities and stimulates microglia to suppress production of A β [75]. NFT appear early in the LC as a result of aging, MCI, and in AD [69]. Loss of cells in the LC may therefore induce an age-related impairment of the blood-brain barrier (BBB), thus implicating age-related vascular factors in AD [95,120].

Genes

Despite problems in interpreting early studies of familial cases, including biased recall by relatives and the identity of the actual disorders involved, there was consistent evidence that first-degree relatives of AD patients had themselves an increased risk of dementia [76]. That the degree of the genetic link also varied among individuals was emphasised in an early study by Heyman *et al.* [79] who reported that late-onset cases had a risk of a family history no more than the general population and that a substantial number of cases were not likely to have a primary genetic basis. When Henderson's [76] review was published, however, there were no data on the specific genes likely to be involved in AD. Subsequently, a small number of genes have been identified as causal and many others as possible risk factors.

APP

In the early 1990s, strong evidence emerged of the connection between some rare forms of EO-FAD and specific genetic factors, small numbers of cases being linked to mutations of the *APP* gene [39,58]. Cleavage of *APP* results in the formation of a variety of A β peptides [67], the most common being Ab₁₋₄₂, found largely in SP, whereas the more soluble Ab₁₋₄₀ is also found in association with cerebral micro-vessels [135] and may develop later in the disease [42]. In addition, mutations of *APP* within the A β coding region may result in the deposition of Ab₁₋₃₈ in ves-

sel walls, especially in cases with extensive cerebral amyloid angiopathy (CAA) [138]. Early soluble peptide oligomers could also be involved [56], which vary with the type of mutant, thus providing a genetic basis for variations in pathogenesis in FAD. The discovery of A β led ultimately to the ACH [72] (Fig. 1) and therefore, risk factors which modify *APP* metabolism have been given considerable prominence in AD. For example, genome-wide association studies (GWAS) report large numbers of genes with a functional impact on *APP*, with at least 832 genes having the property of moderating *APP* metabolism, eight of which occur within known AD susceptible loci [38]. These genes include the 'fermitin family homolog 2 gene' (*FERMT2*), a β -3-integrin co-activator, which is significantly associated with variations in A β in cerebral spinal fluid (CSF) [38]. Under-expression of this gene may elevate A β by raising the level of mature *APP* and facilitating its recycling at the cell surface. In addition, ATP-binding cassette transporter A1 (*ABCA1*) gene may have a role in A β deposition and clearance and may be associated with some variants of AD [105].

PSEN1/2

The most common form of EO-FAD is associated with mutations of the *PSEN1/2* genes [112,170]. Full length *PSEN* is composed of nine trans-membrane domains located on the endoplasmic reticulum. Endoproteolytic cleavage of *PSEN* and assembly into γ -secretase complex is followed by transport to the cell surface, thus potentially influencing *APP* processing [85]. Mutant *PSEN1* may interact with *APP* by enhancing 42-specific- γ -secretase cleavage of normal *APP* resulting in increased deposition of A β [182]. Nevertheless, *PSEN* may have a variety of other functions. First, it may act via loss of function by a reduction in γ -secretase activity [199]. Second, the *PSEN1* gene may be involved in notch signalling and may therefore be important in cell differentiation [179]. Third, *PSEN1/2* may be involved via the perturbation of cellular calcium homeostasis [202] or in interactions with the transcriptional coactivator cAMP-response element binding (CREB-binding) protein which plays a key role in regulating gene expression [49]. Fourth, *PSEN1* may mediate neuro-protective functions by ephrin-B [23] and a decline in such protection could be involved in AD. Hence, there may be features of the action of *PSEN1* not directly related to *APP* metabolism.

APOE

Several studies have emphasised the importance of genes involved in cholesterol transfer as risk factors for AD such as *apolipoprotein E (APOE)*, *apolipoprotein C1 (APOC1)*, and *apolipoprotein J (APOJ) (clusterin)* suggesting deterioration of cholesterol homeostasis [110]. Allelic variation in the *APOE* gene is a major risk factor in SAD, individuals with AD having 2-3 times the frequency of allele $\epsilon 4$ compared with normal control cases [166,181]. In addition, the presence of $\epsilon 4$ may directly affect cognitive function being associated with reduced test scores on adult learning tasks involving memory and learning [116]. Allele $\epsilon 4$ may accelerate the development of AD pathology within the aging brain [143] and hence, is often associated with an earlier disease onset [61]. The majority of studies also report increased A β deposition in individuals expressing $\epsilon 4$ [25,29,149]. In addition, peripheral inflammation, APOE and A β may interact to induce cognitive decline and cerebrovascular dysfunction [123] and in transgenic mice, $\epsilon 4$ markedly facilitates age-dependent CAA [51].

Other genes

APP and *PSEN1/2* genes together account for less than 5% of all AD cases [66,83]. Hence, GWAS have also revealed AD-associated genes on chromosomes 6, 9, 10, 11, 12, 14, 18, 19 [34,172]. The gene on chromosome 12 [145] was mapped to 12q13, a region which encompasses the *vitamin D receptor (VDR)* gene [193]. This gene is a major mediator of the activity of vitamin D and insufficiency of this vitamin could therefore be linked to AD. In addition, a gene polymorphism at 9p21.3 may affect susceptibility to AD in Caucasians [201]. A more recent GWAS indicates 26 novel risk factor genes involving a variety of functions including cholesterol and lipid metabolism, the immune response, and endocytic trafficking [99]. Additional genes which have been reported as possible risk factors include glyceraldehyde-3-phosphate dehydrogenase (*GAPDH*) [5], a rare variant of the triggering receptor expressed on myeloid cells 2 (*TREM2*) gene [161], genetic variation in the estrogen receptor (*ESR*) gene [162], polymorphisms of the clusterin gene [150], and the transferrin (*Tf*) gene [194]. The *TREM2* gene is involved in triggering receptor expression on myeloid cells, and upregulation of the gene has been demonstrated in frontal cortex but not in the HC in SAD [146].

Epigenetic factors

Epigenetic factors, i.e., heritable changes in gene expression which do not involve DNA coding sequences, have also been identified which may alter allelic expression in a significant number of the genes involved in AD [106]. Hence, Lahiri and Maloney [107] have proposed a 'dual hit' hypothesis in which epigenetic changes early and later in life summate to result in AD, a hypothesis which will be described in more detail in a later section.

Metals

Virtually the only metal considered by earlier reviews as a risk factor for AD was aluminium, exposure to which was considered then, and remains today, controversial [10,12,13]. Since the 1980s, there has been more general concern regarding metal exposure as the ability of cells to efficiently maintain key processes with age, such as energy production, repair, and regeneration, is dependent on a range of metals [156]. In addition, a significant proportion of the population are routinely exposed to trace metals such as aluminium, lead, iron, and copper, obtained from a variety of sources, and all are potential risk factors for AD [86]. Arsene *et al.* [16], however, reported no relationship between metal accumulation with age or neurodegeneration suggesting the brain was not a favourable site for metal accumulation.

Recent data suggest that: 1) a large number of metals could be implicated in AD pathogenesis, 2) there may be interactions among different metals, and 3) metal imbalance leading to lack of cellular homeostasis could be an important factor. Regarding the individual metals, more recent studies of aluminium report significantly increased mortality from AD among miners exposed to aluminium-rich dust [147] suggesting that some aspects of this hypothesis might be worth revisiting. In addition to aluminium [195], zinc [127,192], mercury [140], copper [86,144], manganese [45,186], cadmium [136,142], and magnesium [188] have all been suggested as risk factors for AD. Many of these metals have been shown to interact directly with APP metabolism or with APOE [140]. Studies have also emphasised the synergistic effects of different metals. Hence, a mixture of arsenic, cadmium, and lead increased A β deposition in frontal cortex and HC in young rats by increasing APP and activating the pro-amyloidogenic pathway [17]. However, realistic intakes of

a mixture of aluminium and zinc did not accelerate AD-type pathology in a double transgenic mouse model (APP, tau) [3]. A key process which becomes dysregulated with age is metal homeostasis [2] and imbalances among essential trace elements together with exposure to other metal ions, may result in AD pathology. Hence, AD plasma/serum and brain is characterised by lack of homeostasis among zinc, copper, and iron all of which are involved in the regulation of APP/tau and also interact with APOE [200].

Traumatic brain injury

Henderson [76] quoted three studies suggesting increased frequency of traumatic brain injury (TBI) in the previous history of AD patients [80,139,169]. TBI could cause damage to the BBB resulting in leakage of plasma proteins and sensitization of the immune system to brain antigens normally isolated from them. Subsequently, a number of studies reported a connection between head injury and AD. In survivors of head injury, APP is observed in neuronal cell bodies and in dystrophic neurites surrounding A deposits, as observed in AD [54]. Subsequently, it was shown that specific neurons in the medial temporal lobe (MTL) secreted large quantities of APP and that there were more APP-immunoreactive neurons in these areas in TBI [132]. Hence, increased expression of APP in head trauma cases may be an acute-phase response to neuronal injury [156], the overexpression of APP leading to the deposition of A β . Several acute-phase proteins are localised within A β deposits in AD including amyloid-P, complement factors, and α -antichymotrypsin [96]. Furthermore, Regland and Gottfries [153] proposed that APP maintains cell function by supporting neuronal growth and survival. The possible neurotrophic action of APP is also supported by the observation that it shares structural features with the precursor for the epidermal growth factor. Moreover, NFT may be part of the neurons response to injury [198].

The relationship between TBI and AD is further emphasised by the discovery of the tauopathy chronic traumatic encephalopathy (CTE), a neurodegenerative disorder believed to result directly from repetitive brain injury [53,93]. Hence, CTE has been recorded in association with contact sports including boxing, American football, ice hockey, and wrestling [122] and has also been reported in military veterans exposed to blast shock waves from explosive

devices [60,129,130,171]. Clinically, the symptoms of CTE resemble those of AD and include impairment of memory and executive function, behavioural change, disturbances of mood, and the presence of motor symptoms [163,180]. The neuropathology of CTE also overlaps with that of AD [122]. Hence, CTE cases exhibit reduced grey matter volume in several brain regions, most prominently the frontal and anterior temporal lobes associated with enlargement of the lateral and third ventricles [129,131]. CTE as a tauopathy has a spectrum of tau-immunoreactive pathology which varies from focal, perivascular NFT in frontal cortex [100] to a more widespread and severe tauopathy affecting temporal lobe, limbic system, and the striato-nigral system [129]. The isoform profile and phosphorylation state of tau in CTE is also similar to that of AD in that both three-repeat (3R) and four-repeat (4R) tau are present in equal ratios [204]. NFT and neuropil threads (NT) can be observed in affected areas together with comorbid AD neuropathologic change (ADNC) in the form of A β deposits [64,91], and astrocytic tangles (AT) [163,177]. Whether CTE is a distinct tauopathy or a subtype of AD linked specifically to head trauma remains to be established.

Diet

Apart from malnutrition and calcium deficiency, dietary-related factors were not particularly emphasised in earlier reviews [74,76,79,80,109]. Nevertheless, more recent research has identified a number of such factors for AD and specifically the importance of obesity, variation in diet, and diabetes.

Malnutrition

Abalan [1] was one of the first investigators to propose that malnutrition could be a risk factor for AD. This hypothesis was based on clinical observation of AD patients who often exhibited emaciation and cachexia, urinary tract infections, terminal bronchopneumonia, and low triceps skinfold. Low serum albumin, iron, folate, tryptophan, vitamin B12, and cerebral metabolism of glucose and oxygen were also present. These symptoms suggest a 'protein-calorie malnutrition syndrome' in AD which could result in the development of NFT due to a chronic nutritional deficiency of calcium/magnesium. In addition, marked deficiency of vitamins E, A, D, and K has been observed in plasma in AD suggesting that regular supplements might enhance cognition and reduce A β deposition

[68]. A problem with this type of hypothesis, however, is in separating cause and effect, as malnutrition or various deficiencies might also be the consequence of AD, viz., resulting from either the mental state of the patient or physiological changes within the body secondary to AD [1].

Variation in diet

One of the first demonstrations of a link between diet and AD was by Sparks *et al.* [176] in which deposition of A β was induced in rabbits fed with high levels of dietary cholesterol. Moreover, although dietary cholesterol does not normally cross the BBB, in cholesterol-fed rabbits, both enlarged ventricles and a reduction in cerebral vessels were observed [168]. Using a triple transgenic mouse model, high fat consumption combined with a lower polyunsaturated fatty acid ratio also promoted A β and a tau-immunoreactive pathology similar to that of AD [94]. Moreover, statin use may reduce the risk of AD independent of the possession of *APOE* allele ϵ 4, but the strength of this link reduces with age [113,126]. McCaddon and Kelly [126] found in a human family carrying an *APP*₇₁₇ mutation, that individuals with AD had a greater vitamin B12 deficiency compared with unaffected members. This link was unlikely to be a consequence of impaired dietary intake; additional evidence that vitamin B12 deficiency could be a risk factor for AD. There is also evidence that vitamin D deficiency and consequent homocysteinemia could influence both the progression of neurodegeneration and the degree of vascular pathology [137]. Hence, in dementia cases, vitamin D deficiency, low levels of folate, and high levels of homocysteinemia were more pronounced in cases with subcortical vascular dementia (VaD). The synergistic effects of malnutrition, oxidative stress and homocysteine-related vitamins in AD were also emphasised by von Arnim *et al.* [189]. Nevertheless, the impact of nutritional supplements in early and late AD using B-vitamins and antioxidant vitamins has been inconclusive. Wang *et al.* [196] studied the influence of diet and cognitive function in individuals with MCI in a large cohort of Chinese patients and revealed a link between inadequate consumption of legumes and animal oil, other food items having no significant association.

Obesity

Whether obesity is a specific risk factor for AD has been controversial. Of 14 different risk factors

associated with cognitive impairment in a large sample of cases, depression, obesity, and hypercholesterolemia were more likely to be associated with a low AD risk, only alcohol use increasing the risk of cognitive decline [31]. The study also concluded that many of the 'traditional' risk factors for AD were not associated with early AD or its progression. By contrast, a strong correlation between obesity and the development of AD has been observed suggesting that metabolic changes associated with obesity damage the nervous system leading to neuronal death by apoptosis or necrosis by altering the plasticity of neurons [125]. Obesity has been consistently associated with the presence of dementia, higher midlife body mass index (BMI) proportionally increasing AD risk [185]. Moreover, obesity in combination with vascular risk factors was associated with LO-SAD and with various metabolic syndromes involving leptin and adiponectin expression [71].

Diabetes

Insulin has a central role as a neuromodulator [98] and therefore, it is not surprising that diabetes has been linked to AD [4]. First, there is an association between hyperinsulinemia and hyperglycaemia and AD, which is caused by insulin resistance resulting in accumulating SP especially in individuals expressing *APOE* allele ϵ 4 [124]. Second, there is a link between type 2 (T2) diabetes and its precursors, elevated adiposity and hyperinsulinemia, and dementia; the risk evident in middle-aged, but not in older individuals, and greater for VaD than LO-SAD [118]. Third, in transgenic *APP/PS1* mice with severe hyperinsulinemia there was severe brain atrophy, cortical thinning, and elevated caspase levels [151]. Fourth, in experiments using rats fed a high fat diet including cholesterol, there was an increased cognitive decline accompanied by A β deposition in the HC [22]. Fifth, there is an association in diabetics between diabetes-associated genes within the sortilin family of vascular protein sorting-10 domain (*Vps10*) genes and AD, dysfunction of which can lead to A β deposition and insulin/glucose dysfunction [108].

Mitochondrial dysfunction

Although not discussed specifically by Henderson [76], theories suggesting that mitochondrial dysfunction may be involved in AD have a long history [30]. Hence, distorted mitochondria accompanied

by a decline in cerebral metabolic rate are present in early AD [30]. In addition, there is a deficiency of enzymes involved in carbohydrate utilization including such mitochondrial markers as phosphofructokinase (PFK) and pyruvate dehydrogenase [30]. As a consequence, chronic hypoperfusion could induce oxygen stress via the production of reactive oxygen species (ROS) and result in mitochondrial failure and AD [6]. Moreover, part of the familial aggregation of AD may reflect excess maternal versus paternal inheritance consistent with mitochondrial inheritance. The possibility of a genetic origin of mitochondrial dysfunction in AD has also led to the formulation of a 'mitochondrial cascade hypothesis' (MCH), in which it is mitochondrial dysfunction that is the initial event leading to AD pathology [183]. A particularly interesting protein is 'adaptor protein evolutionarily conserved signalling intermediate in Toll pathway' (ECSIT) which may act as a molecular sensor, involved in a cell homeostasis in response to oxidative damage by A β [175]. Protective molecules could then be specifically activated in response and this failure could result in severe mitochondrial damage, promoting apoptosis, and resulting in synaptic dysfunction and neuronal death [175]. A correlation has also been observed between mitochondrial DNA (mtDNA) haplotype and AD, the sub-haplogroup H5 of mtDNA being a risk factor for LO-SAD [165].

Vascular disease

Henderson [76] noted that AD and VaD commonly coexist, 18% of a dementia autopsy series having evidence of both disorders. If AD and VaD are distinct and independent disorders, then the prevalence of their joint occurrence should be the product of their respective prevalence ratios [76]. Nevertheless, the observed prevalence of AD/VaD is usually greater than indicated by this calculation suggesting either that the effects of mild AD and VaD are additive thus increasing the chance of recognition of their joint occurrence or that the ischaemia of VaD accelerates the pathogenesis of AD [76].

Many studies have identified a number of links between AD and cardiovascular disease (CVD) [116]. The integrity of the vascular system is essential for normal brain function and age-related changes in the vasculature result in impairment of autoregulation, neovascular coupling, BBB leakage, and reduced vascular tone [95]. These changes may

precede cognitive decline and in combination with other factors contribute to the neuropathology of AD [95]. Various vascular factors have been correlated collectively with the assessed neuropsychology of AD, but no individual vascular risk factor could predict change in any single neuropsychological feature [178]. In addition, various biomarkers of microvascular endothelial dysfunction are associated with dementia including elevated levels of the vasodilator peptide hormone mid-regional proadrenomedullin (MR-proADM) which is present in all forms of dementia while elevated C-terminal endothelin-1 (CT-proET-1) is only associated with VaD [84].

CVD may result in A β deposition and affect the age of onset of AD while A β may itself trigger cardiovascular degeneration [111]. Individuals with congestive heart failure also have a higher risk of dementia [81] while cerebral ischaemia and stroke may lead to hypoxia, A β deposition, and impairment of the BBB leading to neuronal degeneration [203]. Small infarcts and micro-bleeds are also associated with increasing A β deposition [27]. Finally, blood vessels with collapsed or degenerated endothelia are evident in more than 90% of AD cases [97] and occur concurrently with A β deposition while blood vessels exhibit degenerative changes in AD accompanied by A β deposition and loss of smooth muscle cells [184]. Attems *et al.* [18] found additionally that A β ₄₂ was deposited within the glia limitans rather than capillary walls.

Immune system

Various disorders and co-morbidities associated with AD were discussed in earlier reviews [76] but there was little specific discussion of the involvement of the immune system. Nevertheless, several lines of evidence support the presence of immune system dysfunction in AD [128,141,158]. Hence, complement proteins associated with the 'classical' pathway [141], brain reactive antibodies [128], immunoglobulins [46,88], circulating immune complexes (CIC) in peripheral tissue and cerebral blood vessels [73], helper/inducer and cytotoxic/suppressor T-cells [128], and abundant reactive microglia [128] have all been observed in AD. Complement system proteins may act as pattern recognition molecules mediating the uptake of A β by glial cells, which express complement receptors [187]. In addition, alterations in the major histocompatibility locus (MHC) antigens

have been demonstrated [190] suggesting either increased resistance or susceptibility to a specific antigen in AD [40,77]. Several genes encoding the inflammatory mediators have also been implicated in AD, especially those of HLA class III region [119]. Nevertheless, it is unclear whether the immune response is a reaction to a primary antigen or a secondary response to the deposition of the characteristic AD proteins.

Infectious agents

The possible involvement of infectious agents in AD has long been suggested as a risk factor [89] and the possibility of virus infection was also discussed by Henderson [76]. One of the first studies to suggest that infection could be a risk factor for AD proposed that invasion by herpes simplex virus (HSV), to which antibodies may be observed in cerebral spinal fluid (CSF) in AD, could induce abnormal protein formation resulting in NFT [114]. In addition, invasion by a virus may activate microglia and pericytes ultimately resulting in A β deposition [197]. Such a theory is given further credibility by observations of marked structural and biochemical alterations in regions of the AD brain associated with olfaction, most notably the olfactory bulb and entorhinal cortex [44], the olfactory system being a possible point of entry into the brain for an infectious agent or protein [121]. Hence, viruses introduced into body cavities and organs often result in high titres of the virus in olfactory epithelium, olfactory bulb, and other brain regions. Nevertheless, HSV does not typically enter the brain via the olfactory system [164]. More recently, however, DNA from peripheral blood leucocytes and brain of AD patients has been analysed for *cytomegalovirus* (CMV), Epstein-Barr virus (EBV), and human herpes virus 6 (HHV-6), the data suggesting that EPV and HHV-6 could be risk factors for cognitive decline and progression to AD [35]. In addition, dental infections could be a risk factor [159], a higher prevalence of the disease being observed in those patients with orofacial pain and periodontal infection although these effects could also be secondary to AD. No increase in the incidence of pneumonia has been reported in SDAT although the *Chlamydomphila pneumoniae* bacteria are implicated in LO-SAD [19] and associated with AD pathology [55]. In addition, there are clinical and pathological similarities between syphilitic dementia caused by

Treponema bacteria and AD [133] and evidence that A β may be an 'anti-microbial' peptide [62]. Fungi have also been suggested as a risk factor for AD [7].

Psychiatric factors

The role of psychiatric factors as antecedents to AD was discussed by Henderson [76] who reported negative results from various studies [74,109,173]. Nevertheless, Heyman *et al.* [80] reported that a previous psychiatric morbidity was associated with AD while French *et al.* [50] and Barclay *et al.* [21] both suggested an association with depression. Subsequently, Bannerjee *et al.* [20] investigated whether such associations were due to depression either being a risk factor or a co-morbidity of AD. It was concluded that the coexistence of the two conditions could reflect altered circulating levels of common metabolites such as cytokine K6, TNF- α , and serum 25 hydroxy-vitamin D. Increasing stress in early life has also been suggested as a risk factor for cognitive decline at a later age with evidence that stress may contribute to amyloid pathology in early stressed mice [82]. Piirainen *et al.* [148] also emphasises that chronic psycho-social stress should be recognised as a risk factor for LO-SAD.

Discussion

What are the major risk factors for Alzheimer's disease?

As earlier reviews concluded, there are large numbers of potential and apparently unrelated risk factors associated with AD. That there is a clear association between AD and aging was widely accepted by earlier investigators and is still valid today [155], many of the features of AD pathology being observed to some extent in the aging but cognitively normal brain [154]. In addition, in rodent models of AD, the most important factors influencing the onset of 'AD' are often age-related including: 1) perturbation of ribosomal and oxidative phosphorylation pathways, 2) changes in genes associated with hypothalamic-pituitary-adrenal function, and 3) changes in insulin signalling [90]. Although Henderson [76] discussed family history as a factor, there was little genetic information available at that time. Subsequently, large numbers of genes have been identified in AD, either causal as in EO-FAD such as *APP* [39,58] and *PSEN1/2* [112,170] or associated as risk factors with LO-SAD as a result of GWAS [99],

allelic variation of the *APOE* gene [166,181] being the most significant to date. Moreover, the case for head injury as a risk factor has been strengthened by the discovery of the tauopathy CTE although its relationship to AD is unclear [129-131]. Vascular factors continue to be an important element of the risk supported by many pathological studies of the vasculature [95]. New risk factors have also been identified including those associated with diet such as obesity [31,71,125,185], diabetes [4,118,124] and factors associated with the immune system [12,128,141,158]. With reference to metal exposure, the case for aluminium is less strong but other metals such as zinc and copper have been implicated, and the interactions among different metals emphasised [16,86,147,156]. Recent data have also increased the probability that exposure to infectious agents could be involved [89].

How do risk factors result in Alzheimer's disease pathology?

The challenge posed by these data is the same as that discussed by Henderson [76], viz. how to integrate the epidemiological findings to demonstrate how numerous and disparate risk factors result in AD. The study of risk factors suggests that, with the exception of some rare EO-FAD cases, AD is not primarily a disease linked directly to defective genes but a complex syndrome dependent on the rate of aging and indirectly influenced by many genetic and environmental risk factors and the general health of the patient [101]. In fact any factor which influences the health of an individual through life and the rate of aging could be a potential risk factor.

A number of attempts have been made to formulate hypotheses to explain AD based on risk factors and this review considers three possible approaches to the problem. First, in his synthesis of epidemiological findings, Henderson [76] suggested either: 1) "an accumulation of some toxic substance or a time-dependent effect following prior introduction of a toxic substance or infectious particle" or 2) "an age-related increase in a biological process necessary for normal neuronal function accentuated by environmental exposure and/or genetic vulnerability". It was also concluded that it was unlikely that genetic or environmental factors act directly but that they accentuate some general process that occurs in the brain with age. It was postulated that the common feature associated with many of the risk factors is that they act by promoting the increasing liberation of oxygen free radicals with age which then exacerbate the rate of normal aging ultimately resulting in AD (Fig. 2).

Second, Lahiri and Maloney [107] proposed a 'dual hit' hypothesis to explain AD (Fig. 3), which involves the latent expression of specific genes triggered at the developmental stages of life. Hence, the first 'hit' involves environmental stress early in life acting on gene regulation at sites of promoter genes and mediated by epigenetic changes such as DNA methylation. The second 'hit' involves further stress acting later in life in combination with changes in gene expression. In this hypothesis, it is the interaction between environmental stress, which may involve many disparate risk factors, and genes which is emphasised.

A third hypothesis is based on the concept of the body's 'allostatic load' (Fig. 4) [10,36]. The primary

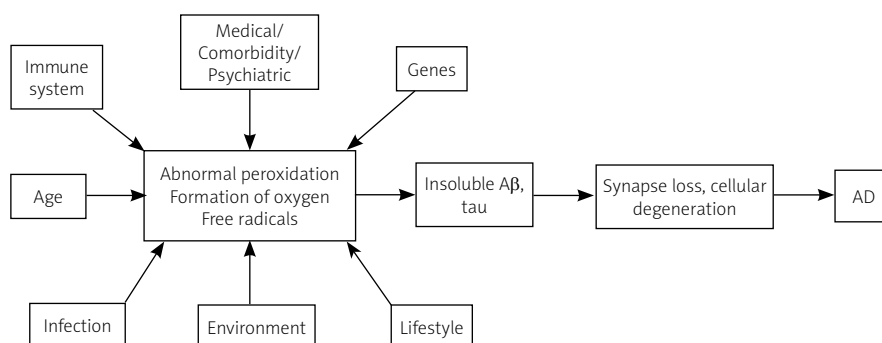
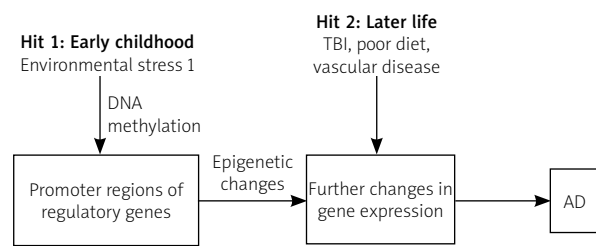


Fig. 2. A scheme based on Henderson's hypothesis [76]. Hence, genetic or environmental factors promote the increasing liberation of oxygen free radicals with age which then exacerbate the rate of normal aging.

risk factor in this scheme is the rate of aging, the age dependent breakdown of anatomical systems, and consequent loss of synapses [36]. The extent of this aging effect, which begins early in life, is mediated by the degree of lifetime stress or allostatic load [36]. The brain is the ultimate mediator of stress-related mortality through hormonal changes resulting in hypertension, glucose intolerance, CVD, and immunological problems [36]. The consequence of these processes is gradual synaptic disconnection, neuronal degeneration, and the upregulation of genes which determine the production of reactive and breakdown products such as A β and tau [153,191].

How could the risk of Alzheimer's disease be reduced?

An inevitable conclusion from the study of AD risk factors and the hypotheses they suggest is that life-style changes need to be implemented over a life-time to significantly reduce the risk of AD. Hence, strategies are required that will slow the rate of aging by reducing the allostatic load. For example, healthy fit middle-age adults tend to have fewer chronic conditions later in life and therefore, a lesser burden of chronic disease before death [152]. It has also been suggested that physical exercise can modify metabolism, brain processes, and preserve cognition if suitable structured exercise programs could be developed which are specific to the individual, of sufficient intensity and duration, and which comprise several different components [102]. There is also growing evidence that increased cognitive activity through life could reduce the risk of AD [92,174]. Three factors may influence cognitive performance



AD – Alzheimer's disease, TBI – traumatic brain injury

Fig. 3. The 'dual hit hypothesis' [107] which involves the latent expression of specific genes triggered at the developmental stages of life. Hit 1 involves environmental stress early in life acting on gene regulation at sites of promoter genes and mediated by epigenetic changes such as DNA methylation while hit 2 involves further stress acting later in life in combination with changes in gene expression.

in later life: 1) the level of education, 2) occupational complexity, and 3) the degree of cognitive leisure activity [92]. In a study of the effect of these variables on cognitive performance of middle-aged adults at risk of AD, it was shown that some of the variance attributed to education was closely related to the degree of cognitive activity [92].

Evidence that dietary changes can reduce the risk of AD has been more controversial. In Japan, for example, the rate of AD has risen markedly in the last decade associated with increased consumption of alcohol and animal products and a reduction in 'traditional' diets [65]. There has also been interest in whether the 'Mediterranean' diet, i.e., a diet rich in vegetables, fruits, fish, and olive oil may be

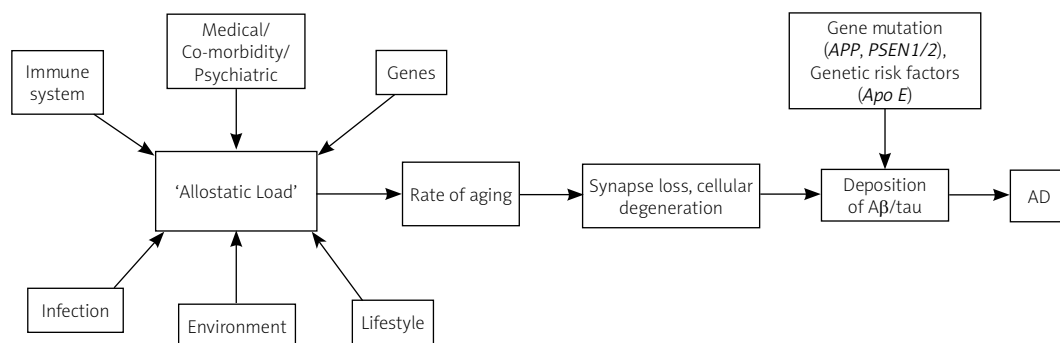


Fig. 4. A scheme of how the various risk factors may cause Alzheimer's disease (AD) based on the allostatic load [10,36]. The various risk factors act cumulatively and in combination to increase the rate of normal aging, leading to degeneration of neural pathways and blood vessels and resulting in the formation of β -amyloid (A β) and tau and then senile plaques (SP) and neurofibrillary tangles (NFT).

protective against AD. Hence, Scarmeas *et al.* [167], in a study involving 2000 participants evaluated every 18 months, showed that those with a higher 'commitment' to the Mediterranean diet exhibited a reduced cognitive decline. In the 'Rotterdam study' involving 5000 participants and followed up after 6 years, a diet high in antioxidants including β -carotene, flavonoids, vitamin C, and vitamin E was associated with reduced AD incidence [47]. There is no current evidence that cessation of smoking reduces the risk of AD. Nevertheless, smoking is regarded as a risk factor for many chronic diseases and is likely to contribute significantly to the allostatic load, although its specific effects on the brain are unclear [37].

In conclusion, many risk factors have been associated with AD including those related to on aging, genes, metals, TBI, diet, vascular factors, the immune system, and exposure to infectious agents. With the exception of some rare EO-FAD cases, AD is a multifactorial disorder in which the effect of external and internal risk factors act collectively to affect common processes such as oxygen free radical generation, gene regulation, or the allostatic load. These processes result in an acceleration of the rate of aging that is the ultimate cause of AD. Life-style changes which act to reduce the impact of these processes is therefore a credible strategy to slow the rate of aging and the risk of AD.

Disclosure

The author reports no conflict of interest.

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