Many paths to Alzheimer's disease: a unifying hypothesis integrating biological, chemical and physical risk factors

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Abstract

Sporadic Alzheimer's disease (AD) is a complex, multifactorial disease. We should therefore expect to find many factors involved in its causation. The known neuropathology seen at autopsy in patients dying with AD is not consistently seen in all patients with AD and is sometimes seen in patients without dementia. This suggests that patients follow different paths to AD, with different people having slightly different combinations of predisposing physical, chemical and biologic risk factors, and varying neuropathology. This review summarizes what is known of the biologic and chemical predisposing factors and features in AD. We postulate that, underlying the neuropathology of AD is a progressive failure of neurons, with advancing age or other morbidity, to rid themselves of entropy, i.e. the disordered state resulting from brain metabolism. Understanding the diverse causes of AD may allow the development of new therapies targeted at blocking the paths that lead to dementia in each subset of patients.

Keywords

Ageing, Alzheimer's disease, neurodegeneration, entropy

Introduction

The recent failures of several clinical trials of anti-amyloid therapies [1] have prompted a rethink of the cause of Alzheimer's disease (AD). The amyloid cascade hypothesis of AD originally owed much to the genetics of familial AD and to the neuropathology seen at autopsy of both sporadic and familial AD [2-4]. However, familial AD mutations in the key genes, *APP, PSEN1/2* and *APOE*, account for < 5% of AD cases [5]. Also, examination of brain pathology at the end-state of AD, i.e., at autopsy, is not necessarily a good guide to what triggers the disease. Nevertheless, much further evidence has since been found in support of the amyloid hypothesis, though considerable evidence has also emerged against it [6]. It has been reasonably pointed out that those therapies were applied at too late a stage of AD development: since AD develops preclinically for decades [6], the anti-amyloid therapies might have been successful if given at a prodromal stage. Hormesis likely applies to amyloid-β (Aβ) functions where excess Aβ are harmful and have a role in the development of sporadic AD, even if it is not the trigger. In contrast, physiological (i.e., picomolar) amounts of Aβ serve a beneficial function. [7-11] However, the purpose of this review is consideration of alternative hypotheses of AD causation, rather than a critique of the amyloid cascade hypothesis.

Sporadic AD is a complex, multifactorial disease. We should therefore expect to find many factors involved in its causation. Indeed, a huge number of factors affect cognitive processes, including: genetics [12] and epigenetics [13], immune [14] and cerebrovascular functions [15], brain volume [16], exercise [17] and even blood group [18]. Similar factors also influence conditions of cognitive decline, such as AD. We might therefore attempt to reduce these factors to a shorter list of those most likely to contribute causally to the initiation and development of AD. To do that we will first examine the main risk factor for AD, namely ageing, since this can trigger the others as we will see below. This explains why most of them can be detected at autopsy. We will then consider if there may be another more fundamental factor underlying those mechanisms. This approach should ultimately lead towards a hypothesis of the causes of AD.

The above begs an important question: does the known pathology cause the dementia? This question was raised by the researchers on the Medical Research Council Cognitive Function and Aging Study [19-21]. They studied over 500 brains from elderly volunteers and found: (i) a substantial population who died with dementia but with relatively little brain pathology (neuritic plaques, tangles, Lewy bodies, hippocampal

atrophy or vascular pathology) and (ii) a group who remained fully lucid till their death but were then found to have significant brain pathology. Similarly, the Honolulu-Asia Aging Study performed 285 autopsies on brains of elderly people and found that, 25% without any dominant pathology had dementia [22]. Another study found that in 169 cases of autopsy-confirmed AD, the total AD pathology (neuritic plaques and tangles) accounted for less than half the variation in the results of several cognitive, functional and psychiatric tests [23]. Moreover, another study [24] found 50 cases with pathology consistent with intermediate or high likelihood of AD [NIA-Reagan criteria] out of 134 autopsies on people without any cognitive impairment. Other studies have reported significant levels of AD-type pathology in elderly individuals without dementia [25-28]. In contrast, a study of 858 autopsied cases (mean age: 88.5 years), who had been followed for up to 20 years, found that the effects of age and *APOE* genotype on cognition could be explained by the studied pathologies (plaques, tangles, infarcts and Lewy bodies) [29]. The balance of all this suggests we may be missing something. Which pathology is truly the causal event?

Evidence from the autopsy studies above also indicates that, in relation to neuropathology, people follow different paths to AD. Below we compile the different risk factors and pathologies that have been implicated in AD causation in recent decades. We postulate that none of these factors alone is sufficient for AD causation and that it is likely an interplay of biological, chemical and physical factors that ultimately culminates in AD dementia (**Figure 1**).

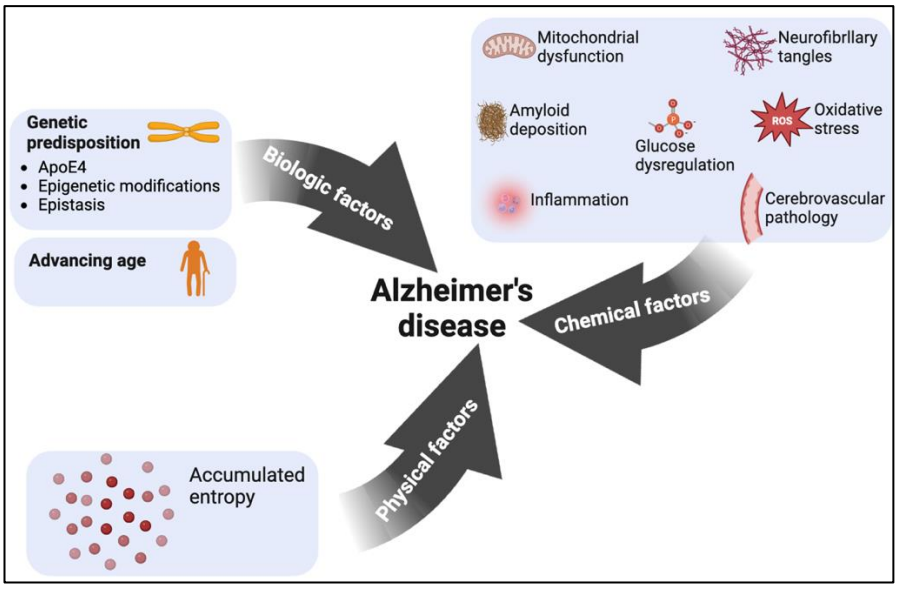

Figure 1. Biologic, chemical and physical risk factors contributing to Alzheimer's disease causation

Alzheimer's disease – distinctions from healthy ageing and Parkinson's disease

Alzheimer's disease versus ageing

Ageing is the strongest risk factor for sporadic AD, but the world contains millions of cognitively sound, very old people. Many of the features of the ageing brain are also seen, often to a greater extent, in AD, e.g.: chronic neuroinflammation [30], oxidative stress [31], mitochondrial dysfunction [32], clearance failures [33, 34], Aβ deposition [35], neurofibrillary pathology [36], decreased olfactory function [37], cerebrovascular degeneration [38] and abnormal neurogenesis. Some of which are described in more detail below. Yet AD is more than accelerated ageing [39, 40]. Ageing is thus an essential background to sporadic AD and it may prime the brain for AD. But ageing alone is an insufficient cause. As such there are clear differences between ageing and AD, not only clinically, but also pathologically [40-42]. Nevertheless, age is the greatest risk factor for AD. Disease prevalence increases worldwide exponentially from the age of 65, roughly doubling every six years of age, from around 2% of people in their late sixties to 35% or more of those in their nineties [43].

How do the main mechanisms of brain ageing compare with the development of AD? Ageing may be defined as an accumulation of partial physiological dysfunctions and disturbed homeostasis in many bodily systems that make the elderly more vulnerable to various stresses (reviewed in [44]). Though its manifestations vary greatly between people, everyone suffers at least some minor declines if they live long enough. Ageing involves changes in virtually all the major bodily systems, e.g., cardiovascular, pulmonary, renal, digestive, hormonal, osteological, immunological, metabolic and neural.

Neural changes may contribute to cognitive decline in ageing [45]. Brain volume, neuronal number, dendritic structure (reviewed in [46]) and white matter [47] all vary by brain region with ageing and in AD. It has been estimated that 10% of neocortical neurones are lost over the human lifespan. Perhaps more relevant to AD development than neuronal numbers are the connections between them, in which dendritic length and branching play major roles and contribute to plasticity and which differ between aged people with and without AD [48-51].

Protein aggregation is a common, though not universal, feature of the ageing brain. Such aggregates, particularly of Aβ, were traditionally regarded as strictly pathological in AD (see below). However, it is now known that a substantial proportion of elderly people, with no measurable cognitive impairment, are Aβ-positive by PET imaging [27, 52]. Indeed, a considerable proportion are found at autopsy to have sufficient pathology to meet the criteria of AD [21, 24]. Amyloid deposition in ageing is accompanied by a slower turnover of Aβ and a loss of soluble Aβ42 [53]. Neurofibrillary pathology is also common in the non-demented elderly [54-56] and even found in younger people, [57] at least in the transentorhinal/entorhinal region [58].

Alzheimer's versus Parkinson's diseases

As stated above there are numerous diseases associated with old age but why do some people develop AD and others, for instance, Parkinson's disease (PD). AD and PD have much in common. They are the two most prevalent age-related, neurodegenerative diseases. They also have mechanisms in common, e.g., neuroinflammation, oxidative stress and the related iron overload. But the clinical presentation differs: AD is by definition a type of dementia, with memory impairment most often the earliest symptom; PD is primarily a movement disorder, though it can lead to dementia in many cases [59]. Further, the pathology is distinct: though both diseases involve neuronal losses, they mainly affect different neurones. In AD, the losses are more widespread and particularly affect pyramidal neurones of the hippocampus and neocortex, as well as noradrenergic neurones from the locus coeruleus and cholinergic neurones from the nucleus basalis of Meynert[60, 61]. In contrast, the most prominent neuronal losses in PD are dopaminergic neurones of the substantia nigra pars compacta and other catecholamine neurons in the brainstem [62-64]. Also, the best-known pathologies in AD, the Aβ aggregates and the tangles containing hyperphosphorylated tau, are not especially noted in PD. On the other hand, α-synuclein aggregation in Lewy bodies is more prominent in PD, though it is also found in some AD cases [65].

While familial (monogenetic) forms of AD and PD account for < 5% of cases, there is a substantial heritable non-monogenic risk component for both disorders of 60-80% of AD [66] and 16-36% for PD [67]. Strikingly, there is little or no genetic risk in common for the two diseases. Thus, the study of the functional effects of the polymorphisms associated with each disease should provide clues to the relevant mechanisms.

The currently replicated genetic risks for sporadic AD involve 22 genes [66] and the genetic risk loci for sporadic PD comprise 27 genes [68]. Notably, *APOE*4 is easily the strongest genetic risk factor for AD, while it is clearly not a risk at all for PD, at least not in Caucasians [69] and this may provide some strong clues to causality and in principle, a similar approach may be applied to the other genetic risk factors for AD and indeed for PD. However, because the risks involved are all relatively weak, and the functional effects of the polymorphisms are still rather poorly understood, such insights are currently limited. However, the study of ageing mechanisms does not explain why ageing is universal and inevitable. To answer that question, we need to go deeper. We need recourse, we believe, to the concept of entropy [70] and that requires a short digression from the usual discussion seen in most neuroscience reviews concerning ageing in relation to neurodegenerative diseases.

Alzheimer's disease – a progressive failure to export entropy?

As we marvel at the vastly complex and beautifully ordered state of the molecules and cells that make up living things, we may wonder how that is compatible with the ever-increasing disorder of our universe. The answer may supply a definition of life: life exports entropy. But life is not unique in this respect. As gases cool and as liquids crystallise, they also export entropy. The proposed definition needs a little more: life *actively and continuously* exports entropy. Organisms continuously seek to minimise their entropy, at the expense of their surroundings. We mean that, since any thermodynamic change must be accompanied by an overall increase in entropy, any entropy reduction in a living system must be compensated by a greater increase in its surroundings. The chemical reactions in our bodies and brains, e.g., in the metabolism of food or propagation of an action potential, involve energy conversions and entropy changes; excess entropy is duly exported. When we cease to export entropy, we are dead.

Entropy theories of ageing have been around for decades [71]. Health is conventionally perceived as an orderly situation; in contrast, diseases are often referred to as 'disorders'. From birth to death, an organism undergoes perpetual reorganization at the molecular, cellular, and organ levels [72]. This reorganization requires energy and is therefore subject to the laws of thermodynamics. According to the second law, all systems progress towards increasing entropy over time. In biological systems this indicates that the

continuous chemical reactions that sustain life incur a dispersion of energy; this energy becomes unavailable to do work and hence is 'wasted'. The energy dispersion results in increased disorder (entropy) within the biological system as the energy required for reorganization becomes limiting. This trajectory of events and progressively increasing entropy inevitably leads to ageing and establishes a limit to life span.

In a seminal 'Views and Reviews' paper in 2006, David Drachman first proposed that differences in the rate of brain entropy progression may underlie the differences between the rates of neurological decline in healthy ageing, mild cognitive impairment and AD [73]. The first author of the current review further postulated shortly before his death in 2019, that AD pathophysiology might reflect, in part, a progressive failure of the neurological system to export (i.e., rid itself of) entropy; and that this failure to export entropy ultimately underlies the specific biochemical changes recognized as causal factors in AD, such as oxidative stress, neuroinflammation and protein misfolding and aggregation that impair neurological function.

Since the illness and untimely demise of the first author, one research group has made progress in quantifying a discrete aspect of brain entropy, namely entropy of the brain signal using resting state functional magnetic resonance imaging (fMRI) and linked it to cognitive traits [74, 75]. In 862 young healthy individuals, entropy of the brain fMRI signal increased with age [75], and lower entropy predicted greater regional activation and deactivation in relation to 5 cognitive tasks, namely emotional, gambling, relational, language and working memory tasks [74]. However, this measure of signal entropy appeared to decrease, rather than increase, in advanced AD, which the authors likened to the reduced brain entropy in sedation and coma states [75].

Development of methods for quantification of other aspects of brain entropy is clearly needed. The contribution of cellular energy deficiency, specifically linked to defective glucose utilization and mitochondrial dysfunction, to AD causation has been more extensively studied and conceptualized and was recently reviewed [76]. The brain has a phenomenally high energy requirement (>20% of total body oxygen and glucose consumption) relative to its size (2-3% of body weight). As is true of other organs, the mitochondrial electron transport chain that mediates oxidative phosphorylation, is crucial for ATP supply to neurons. This enzyme complex sustains damage with ageing and even more accelerated damage with neurodegeneration, in the form of oxidative and nitrative stress (reviewed in [77]). The premise that neurodegenerative diseases ultimately result from a progressive failure of mitochondrial bioenergetics

resulting from oxidative stress, with ATP becoming limiting for exporting entropy, is gaining attention [77-79]. Numerous reports of deficits in the mitochondrial electron transport chain have been described in neurodegeneration, linked to accumulating oxidative stress. Early studies showed decreased activity of neuronal cytochrome oxidase in autopsied brains from AD patients vs. controls [80]. Subsequently, ATP synthase, the key enzyme complex responsible for harnessing the generated energy as ATP showed decreased expression and activity in animal models of AD, in conjunction with increasing oxidative stress [81].

The paradigm of defective energy metabolism in AD unites the oxidative stress and entropy theories of neurodegeneration and offers a plausible avenue for therapeutics. In a mouse model of neurodegeneration [82], targeted mitochondrial delivery of nitric oxide, an initiator of mitochondrial biogenesis was recently shown to enhance ATP production and cytochrome C oxidase activity, and to improve memory performance However, the science of pharmacologically targeting mitochondrial bioenergetics in neurodegenerative diseases to limit the progress of entropy, although gaining momentum, is in its infancy. As this field progress, the development of the methods for quantification of brain specific aspects of entropy at the molecular level, and their responsiveness to treatment will clearly be needed. More work is also needed to map the spaciotemporal relationships between progressive brain entropy as a physics phenomenon in patients destined to develop AD with the better-studied cellular and molecular biochemical processes underlying AD.

Biochemical features underlying AD neuropathology

For many years the chief defining feature of AD was a particular density of extracellular, β-amyloid-containing, neuritic plaques in certain brain regions, as described in the CERAD criteria [83]. More recent criteria, e.g. NIA-Reagan [84], have given equal weight to Braak neurofibrillary stages [85]. Neurofibrillary tangles, largely composed of tau, show stronger association with disease severity than Aβ plaques [86]. Notably, Aβ and tau have physiological roles that have been much less studied than their effects. This is partly evident by their conservation throughout evolution. Aβ is involved in a number of processes including learning and memory, [87] angiogenesis, [88] neurogenesis, [89] injury repair, [90] antimicrobial peptides,

[91] tumour suppression [92] and blood-brain barrier function. [93] Likewise, tau plays a role in a range of biological processes including myelination, [94] glucose metabolism, [95] iron homeostasis, [96] neurogenesis, [97] neuronal excitability [98] and DNA protection [99] in addition to the classic role as a stabiliser of microtubules. [93]

Is the deposition of Aβ, therefore, a compensatory mechanism to lower entropy in the face of cellular threats? There is some evidence that Aβ deposition is accompanied by loss of soluble Aβ42 [53]. However, Aβ and tau aggregates are not the sole characteristic features of AD. Another invariable feature of AD is neuroinflammation, involving the activation of microglia, the secretion of pro-inflammatory cytokines and the activation of complement [100]. Neuroinflammation was once considered to be largely a reaction to the supposed dominant pathology, i.e., plaques. It is now appreciated that inflammation is itself one of the drivers of AD pathogenesis [101]. A closely related process, oxidative stress, is a common feature of AD, particularly in the early stages [102]. Mitochondrial dysfunction is also a feature of AD and can contribute to the excess levels of free radicals [103].

Vascular disease, particularly small vessel disease, is common in AD [104, 105] together with cerebral amyloid angiopathy [106]. Cerebral blood flow therefore decreases in some brain regions in AD [107]. Permeability of the blood-brain barrier increases with age and further increases in AD [108]. The neurovascular unit is dysfunctional in AD [109]. Small vessel disease can lead to white matter damage [110]. Such damage contributes to cognitive decline, both in dementia and in non-demented elderly people and certain vascular factors in middle age, e.g., hypertension, contribute to the risk of AD [111]. But they may not still be seen once clinical AD emerges [112]. Other pathological features of AD include, glucose hypometabolism in some brain regions [113], disrupted insulin metabolism [114], disrupted lipid metabolism [115], including that of cholesterol [116], metal ion dysregulation (e.g. calcium, copper, zinc and iron) [117], neurotransmitter losses (e.g. acetylcholine and noradrenaline) [118], excessive neuronal excitation [119], membrane damage [120], axonal transport problems [121], DNA damage [122], loss of growth factors [123], neuronal cell cycle re-entry [124], TDP-43 pathology [125], dysregulation of micro RNA [126], epigenetic changes [13], telomere shortening [127], prion-like spreading of toxic proteins [128],

failure of degradation systems (ubiquitin-proteasome and autophagy-lysosome) [129], loss of perivascular lymphatic drainage [130], failed neurogenesis [131] and much else.

The ultimate effect of all these pathologies is neurodegeneration, i.e., the degeneration of neurites, the loss of synapses, the death of neurones and atrophy of the brain. This neurodegeneration is believed to lead to the severe clinical effects seen in AD, i.e., cognitive, functional, psychiatric and behavioural deficits.

Determining the possible role of entropy in these pathologies and establishing that there is a severe decline in the export of entropy in AD will clearly involve a great deal of study [132]. Nevertheless, the balance of the evidence cited above suggests we may be missing something. Besides, why should we expect the end-state, i.e., the pathology found at autopsy, to explain the triggering process? However, available evidence suggests that at least some of the factors mentioned above are involved in the initiation of AD, and that the initial pathology will vary in different individuals. That is, many paths lead to full-blown AD; there is no single starting point, no unique cascade to sporadic AD. Different patients will have followed different paths.

What is the evidence for this proposition? The main evidence is that, if we examine the pathologies that characterise AD, many of them interact. That is, one can lead to the other and vice versa. For instance, excess Aβ can induce oxidative stress [133], which in turn can promote the build-up of β-amyloid, especially β-amyloid-42 [134]. It is similar with Aβ and inflammation [135] and indeed with inflammation and oxidative stress [136], i.e. each pathology can promote the other. Oxidative stress can be due to mitochondrial dysfunction and can cause such dysfunction [137] and similarly with excess Aβ and mitochondrial dysfunction [102]. Excess brain iron causes oxidative stress, which induces inflammation, which promotes iron accumulation [138]. Inflammation promotes tau pathology and vice versa. [139] Excess Aβ can cause vascular damage, including atherosclerosis [140], which can lead to inflammation, oxidative stress and raised levels of the amyloid precursor protein *(APP)*, which can generate β-amyloid. [140] Oxidative stress induces Aβ aggregation and tau hyperphosphorylation and vice versa [141-143]. Aβ can also raise the levels and activity of the enzyme, *BACE1*, which helps to generate β-amyloid. [144] Excess Aβ can also increase *APP* metabolism directly [145] and thus generate more β-amyloid. Toll-like receptor 4 (TLR4) signalling can promote the accumulation of β-amyloid, which can increase TLR4 expression [146]. Tau pathology interacts with dysregulation of cholesterol metabolism [147]. Inflammation can induce insulin resistance, which can

lead to oxidative stress and inflammation [148]. Inflammation can promote tau pathology, which in turn can mediate inflammation-induced neurotoxicity [149]. Notably, systemic inflammation has been associated with much more rapid cognitive decline in AD [150] and an exaggerated inflammatory response due to microglial priming [151]. Downregulation of acetylcholine promotes inflammation, which induces endogenous anti-cholinergic activity, both centrally and peripherally [152]. Inflammation can also induce dysregulation of calcium levels, which can promote various AD-type pathologies [153].

Progression of Alzheimer's disease is full of such interactions and vicious circles and there are clearly numerous possible starting points that can lead, in susceptible cases, to the group of pathologies that characterise AD.

Conclusions

It is well known that linking cause and effect is fraught with problems, not least in biology. AD provides a striking example. Nevertheless, we have limited hope of preventing or treating the growing AD pandemic if we fail to understand the causes of this multifactorial disease. So, the attempt must be made. The broad causes are well understood, i.e., ageing, lifestyle and genetic predisposition. But we must be more specific. We therefore suggest that a more integrated approach that incorporates data from multiple sources and scientific disciplines, one that distils the apparent disparate findings into a focussed view to enable the causes to be understood and hence effective treatments devised. Current attempts have often failed, most likely because they target one specific element of the disease (e.g., clearing amyloid deposits) but neglect to address other features of the pathological process. This is not helped, though understandably so, by the way and clinical trials and to a lesser extent basic research are designed. Research focuses on a single drug that engages a single target. Combinations of drugs affecting multiple systems are difficult to test, regulate and generate profit from, but are likely necessary for treatment of AD

We have seen that there are three levels of causation of AD, broadly based in turn on biology, chemistry and physics and all are intrinsically linked. First, there are biological susceptibility factors, both hazardous and protective, such as genetics, ageing and lifestyle factors, e.g., diet, smoking, drinking and physical, mental and social activity. Second, there are chemical mechanisms, including free radicals, proinflammatory cytokines, glucose hypometabolism, Aβ oligomers and dysregulated tau. Underlying all these factors is the

age-related failure to sustain life by exporting entropy. We postulate that all complex diseases of ageing may share that failure and while the laws of physics cannot be altered to slow or reverse ageing some risks can be mitigated such as lifestyle factors. Furthermore, advances in gene therapy may further reduce risk from genetic factors. A greater understanding of the many potential causes of AD should lead to the development of strategies to prevent AD and perhaps even lead to the identification of effective measures that will treat AD.

CRediT authorship contribution statement

Donald Lehmann: Conceptualisation, Writing – original draft preparation; Amany Elshorbagy: Writing – reviewing and editing; Michael Hurley: Writing – reviewing and editing.

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Conflicts of interest

The authors have no conflict of interest to report.

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