Synergy between depression and Alzheimer’s disease: A spectrum model of genomic vulnerability with therapeutic implications

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Abstract

We have previously postulated that Alzheimer’s disease (AD), mild cognitive impairment (MCI), and accelerated aging progress with similar molecular signaling and are a result of genomic vulnerability. Chronic depression—nothwithstanding comorbidities—may also enter the same pathways due to mutant alleles in the depression associated genes such as neurotransmitter-serotonin transporter proteins, e.g. 5-HTT. When depression, AD, and MCI are predisposed due to genomic vulnerability, molecular cascades for the illnesses may combine. Thus, phenotypes may reinforce each other and present an enhanced pathogenic intensity. We suggest that this model can highlight the genotypic and phenotypic interactions of these two neuropathologies and can be used to create new treatment approaches.

Introduction

We have noted that there seems to be a linked pattern in the appearance of neurobiological and clinical phenotypes for depression and AD, in earlier works [1-3]. Since neuromolecular communications are quite similar in the two pathologies, we propose that primary pathogenetic factors lie more in the genome. Although this hypothesis may create more ambiguity, it was possible for us to engender a framework for AD and depression (with or without sequelae) that uses an interaction of a particular molecular signaling series in the brain. We suggest oxidative stress as a pivotal factor.

Modeling a new spectrum from previous works

A convenient angle to our understanding of depression is provided by Akiskal’s new psychobiologic paradigm of depressive illness [1-4], which expounds upon a “spectrum” of depressive severity (from sub-syndromal to syndromal) on which symptoms are expressed (in terms of degree or scale). As such, even sub-threshold manifestations of depression have significance and progressively acquire clinical relevance in a gradient fashion.

The paradigm holds significance in its ability to define depression as an inclusive, syndromic illness with a full spectrum of symptoms such as sub-symptomatic disease, dysthymia, sub-threshold major depression, and major depressive disorder, as well as risks such as psychosis, suicide, bipolar, and manic disorder. Influenced by Akiskal’s model, we suggest a spectrum for Alzheimer’s disease—an illness that at its inception is largely asymptomatic, sparked by genomic vulnerability, and presents few cognitive, motor, or affective impairments. One may say this is the sub-symptomatic or sub-syndromic stage on the spectrum. The sub-threshold phase could be the presence of mild cognitive stressors that progress with age.

With increasing age, cognitive and some emotional signs appear more clearly and progressively—termed aging cognitive impairment (ACI) and mild cognitive impairment (MCI), clinical stages that have very wide ranges of intensity and may sometimes confuse physicians [5].

Lastly, the spectrum will lead to characteristic AD symptoms, which are consecutively more precarious till death. Previously we have discussed the possibility that perhaps AD is not an anomalous disorder but rather the body’s natural progression of an extended lifespan [1]. We can label that the Senility of Alzheimer Type (SAT), which is the most common clinical phenomenology of people age 88 and over [1,3,6,7]. SAT contrasts the Senility of the non-Alzheimer Type (SNAT), which is an uncommon clinical phenomenology of people age 90 and over [1,6,7]. In an effort to delineate this idea, we analyzed a fictitious sample of individuals ages 88-90 who do not die at a fixed population of 1000 (N=1000). Following general epidemiology for AD, 5% of the population bears the disease at age 65, 10-25% at 75, 20-25% at 85, and 35-50% at 100. (AD incidences in SNAT elders are discounted.) Peculiarly, at the last age group we would have an 80% probability for SAT and 20% probabilities for SNAT. Following this trend, if people lived even longer, we can extrapolate that there would be an even lower chance for SNAT. Since most individuals die between the ages of 78 and 85, data skews as a result of a changing sample size. Therefore, MCI and AD prevalence is miscalculated, which affects our perception of the nature of the two neuropathologies.

In sum, for a population of 1000 seniors age 65 without any present

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Ca²⁺, reactive oxygen species and a seven fold increased incidence
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when synthesized by mutant alleles, leading to altered reuptake [12].
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by function of RNA, DNA, enzymes, metabolism, and mitochondria,
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Pathology in depression is closely linked to AD and MCI by way of
stress. 5-HTTs (serotonin transport proteins) can be defective
when synthesized by mutant alleles, leading to altered reuptake [12].
Serotonin depletion leads to increased CRF/cortisol, glutamate,
Ca²⁺ reactive oxygen species and a seven fold increased incidence
of depression [13]. Free radicals enter oxidative stress pathways and individuals can develop AD or worsen a pre-existing instance of either AD or depression. If molecular signaling in depression is a form of ”transverse cross-talk signaling” then signaling is a function of genomic integrity, as noted in Akiskal’s depression spectrum which may interact with pre-existing AD of note, neuromolecular and neurochemical signaling in patients with AD is tenuous and permanent, and depression can accelerate this process. As mentioned earlier, we propose an analogous Akiskal’s scale for AD in the order of: aging, cognitive aging disturbance, MCI, sub-threshold AD, clinical AD, and terminal AD. The natural process is in the form of ”progressive longitudinal signaling,” which spans one’s lifetime, from birth to death [14]. However, genomic vulnerability, free radicals, depression, psychosocial stressors, and PTSD, among others, [12,15,16] may cause an unnatural progression of AD earlier than usual.

Discussion about the role of depression

Phenotypically, depression may present at any age, save for infancy, and appears or disappears at various times in life [4], perhaps with the advent of second generation antidepressants like SSRI’s [13]. In individuals ages 0-30 oxidative stress, which we previously proposed is a major factor for AD and depression, is controlled by neuro-antioxidant defense systems, such as enzymes, vitamins, and chaperone proteins [14].

However, in the middle ages of 30-60, metabolic processes, cellular and molecular signaling in the mitochondria [17], and DNA/RNA repair without transcription bias play a role in healthy metabolism and preventing oxidative stress. As these pathways become more prone to error, reactive oxygen and nitrogen species increase in concentration, which further damage mitochondrial DNA, RNA, neuronal and glial proteins, lipids and carbohydrates, all of which are exacerbated in the presence of genomic vulnerability [18]. Neural antioxidant defense agents and buffers increase resistance to damage from oxidative stress to valuable cellular machinery. Particularly, AβPP, PS1, PS2, tau, and ApoEε4 increase in concentration in the presence of oxidative stress [19,20]. Malfunction of these proteins, which depression may help propagate, leads to the formation of senile plaques and neurofibrillary tangles, a tell-tale sign of AD [21]. However, it is not until the third age group of 60-90 years old that the AD phenotypes appear [20].

In the 60-90 year old age group, clinically relevant symptoms begin to appear. Specific to one’s proclivity for antioxidants in the brain among redox metals, Aβ peptide, hyperphosphorylated tau, and ApoEε4 may be deposited in or around neurons leading to senile plaques [22,23]. There is evidence that the hippocampus [24] and frontal cortex are particularly atrophied by these neurochemical changes brought upon by oxidative stress. Likewise, protease and phosphorylation errors primarily lead to malfunctioning AβPP [19], PS1, PS2, tau, and ApoE [25,26]. In depression, genomic vulnerability [27] enhances this neuromolecular misprocessing in the elderly by interacting with AD signaling pathways that speed up increasing glutamate and Ca²⁺ concentrations, neurodegeneration of the hippocampus, and oxidative stress [15,16,27-31] (Figure 1).

Therapeutic implications

Our suggested model of AD, and its relationship with aging, is more in tune with clinical observations in geriatric patients who present with mild memory impairment but a full range of daily living activities. Without a definitive ability to check for AD till post-mortem [32], this model aims to provide a scale for accurate diagnoses early on.

If a geriatric patient has had a history of depression [33] and memory deficits, then it is a stronger indicator of latent AD. Especially in the case of chronic depression, genomic vulnerability for AD will increase, so preventative measures should be taken before debilitating symptoms appear. If a patient is a carrier of AD, then the physician should scan for attenuated symptoms along the “depressive cross-talk scale,” and may have to employ measures for activated AD or resultant dementia. The treatment team can then find contraindicators for accelerated aging, MCI, and classic chronic depression.

Treatment of other depressive episodes at any stage in one’s life, such as MDD, should also be considered as indicators of a quicker onset of AD. Traumatic brain injury, PTSD, accelerated aging [34], and psychosocial decline can be addressed with cognitive behavioral therapy, lifestyle changes, and medications. A psychiatrist may recommend antidepressant SSRI’s, among others, while a nutritionist may recommend a change to a Mediterranean diet.

Our suggested model consistently addresses accelerated aging, MCI, and AD by tying depression pathways and AD pathology together. Diagnostic imaging studies also support this model as soon

![Figure 1. Diagram illustrating the transition of natural aging to terminal AD through sequential transformation based on Akiskal’s scale](image-url)
as there is significance in the results. We firmly hold that future research focused on this model can provide a better understanding of the nature of these neuropathologies and will shape prevention in the future.

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