Basis and Argument into the Work ‘‘Parallels on Depression and Alzheimer’s Disease and Different Genomic Vulnerability Leading to Therapeutic Utilities’’

Roberto Rodrigues¹*, George Perry² and Robert Petersen³

¹College of Sciences, The University of Texas at San Antonio, USA
²Department of Pathology, Case Western Reserve University, USA
³Department of Biology, The University of Texas at San Antonio, College of Sciences, USA

*Corresponding author: Roberto Rodrigues, R. Rodrigues College of Sciences, The University of Texas at San Antonio, One UTSA Circle, San Antonio, TX 78249, USA. E-mail: neurorob@hotmail.com

Abstract

This synopsis is a brief report about the conclusions in which we have engaged from considering that Alzheimer’s disease, cognitive impairment and aging could progress with analogous molecular signaling, with no frontiers between their phenotypes. We have also proposed that chronic depression, with or no anxiety and/or stress comorbidiindication may interact with these AD manifestations - already product of genomic vulnerability - at any stage of the disease. A known example may be mutant short alleles on the depression genes corresponding to the synthesis of a series of neurotransmitter transporters, particularly 5-HTTs – serotonin transporter proteins - which determine impaired inhibition of 5-HT at the neuron synapse and a decline of serotonin on the brain. AD, cognitive impairment - interacting with aging - has some molecular cascades that may join the Depression cascades and vice-versa when both neuronal pathologies are predisposed together to genomic disturbances, one phenotype reinforcing the other. Also we suggest that this model may be understood and approached by some new therapeutic strategies funded in the genotype and phenotypes interaction of these two illnesses, aging and oxidative stress.

Introduction

Our thesis reportedand are funded on three previous and recent studies [1-3] about the already known and very frequentexpression of concurrent and analogous neurobiological and clinical phenotypes on Alzheimer’s disease and Depression. Its main contents proposed that the essential difference of both pathologies is the genome of each disease, their molecular signaling into the brain being more or less similar and cross-talking with some particularities each. We are conscious that this hypothesis may give origin to a lot of puzzles and enigmas which challenge our work. Anyway, as we show below in a comment about the three works referred, it was possible to elaborate a theoretical model considering an interaction of some neuro molecular signaling series in the brain, amongst depression in general with or notanxiety and stress comorbidities and Alzheimer’s disease. Otherwise, it was proposed that oxidative stress may be the main interaction pathogenic factor between both these entities.

Discussion about the Three Works Referred

The most useful approach to depression was considered by us to be Akiskal’s new psychobiologic paradigm of depressive illnesses [4] that is very consistent as a “spectrum” in which depressive symptoms are expressed in a continuum (degrees or scale) of severity that ranges from sub-syndrome to various intensity grades of syndrome levels. In this Akiskal’s series situation sub-threshold symptoms progressively acquire clinical relevance and gravity or terminal stages of weightiness. This paradigm makes possible to understand depression as a single illness with very variable symptomatic ranging from sub-symptoms disease to dysthymia, to sub threshold major depression and to major depressive disorder with other risky threats as psychosis, suicide, bipolar or manic disorder. Following Akiskal’s psychobiological spectrum model of depression, we have analogously suggested this mentioned paradigm for Alzheimer’s disease, i.e., the disease initiates very early - sometimes in infancy - in the individuals with genomic vulnerability, with neither any symptoms nor any life impairment, be cognitive, motor or affective. We may say that this is the sub-syndrome, sub symptomatic or quoted as previous/ not clinical phase. Progressively with aging, very mild and not significant cognitive distresses start appearing, which we could name sub-clinical or sub-threshold phase. With increasing age, cognitive and some emotional signs appear more clearly and progressively - it would be aging cognitive impairment (ACI) and mild cognitive impairment (MCI), clinical stages that are limitless in the ascendant range of intensity and may sometimes confuse physicians [5]. Finally, the spectrum progresses to the known Alzheimer’s disease symptoms, which also are progressively stronger and most harmful to the individual, only finishing with death. Consistently with our work [1] we considered the following new paradigm in the approaching of Alzheimer’s disease: instead of being the pathological exception of...
and in every depressive crisis molecular signaling interaction with AD signaling, either being processed in normal or through pathological in the AD spectrum, neuromolecular, cellular, and neurochemical may interact with Alzheimer’s disease in progress. Furthermore, metabolic processing in function of the individual’s genomic profile. This means that the various levels of molecular and signaling "transversal cross-talking signaling". This interaction model of AD and aging, without any boundaries in analogy, applied to AD in the following sequence: aging, cognitive aging disturbance, MCI, sub-threshold AD, clinical AD and terminal AD. This could be quoted "progressive longitudinal signaling" which begins in all people with birth and finish with death [14], but in AD genomic vulnerability, as individuals age, free radicals generation [11] and other series of events like diseases, particularly depression, psychosocial stresses, losses, post-traumatic stress disorders [12] etc. may interfere, intensify and accelerate the AD spectrum molecular, cellular and clinical phenotypes. Crisis of depression may happen in any age, except in very young infants; during almost the whole lifespan depressive crises worse and recess in extremely varied ways and periods of time [4], particularly with the use of modern antidepressants in therapy [13].

The Alzheimer’s disease progressive spectrum, genomic vulnerable type, starts practically in infancy periods where it is not identified neither known by anybody. Oxidative stress, in this first life phase – 0-30 years of age – is controlledmainly by the antioxidant defenses of the brain as enzymes, vitamins and other strong antioxidant agents as specific and chaperon proteins [14].

In the middle phase of life – 30-60 years of age– metabolic processes, cellular and molecular signaling in the mitochondria [15], DNA and RNA repairing in case of errors or continuity transcription bioses, are some of the strongest supporters of the brain energetic metabolism. As consequence, reactive oxygen and nitrogen species (RONS) raise to highest levels, damaging mitochondria DNA, RNA, neuronal and glia proteins, lipids and carbohydrates through oxidative stress, particularly in case of genomic vulnerability [16]. The anti-oxidant defense agents, proteins, enzymes and other buffering biochemical and molecular elementsalso elevate to resist either the molecular or cellular damage in the brain. β A-PP, Chaperons PS1, PS2, Tau, ApoE4 and other proteins increase in concentration to avoid oxidative/nitrosative stress from RONS [17,18]. Homeostasis is established when there is no genetic vulnerability, but in case of Alzheimer’s Disease Genomic Vulnerability (ADGV) all these mentioned defense proteins may fail in their protection functions and some senile plaques and neurofibrillary tangles, both the main markers of the disease, may form. Anyway, on this second life phase there are no clinical signs of AD, neither any molecular/cellular phenotype [19]. In case of Depression carrying genomic vulnerability, (DGV) both diseases may interact on the signaling molecular level and progressively worsening the condition till next phase - a conclusion reported on this proposal [20].

On the third phase of life (60 to 90 years of age) AD starts to insert very slowly and increasingly. Soon it will arrive to the clinical stages. At 65/70 years of age, depending on the potential of the patient’s natural brain profile of anti-oxidants, Aβ peptide, hyperphosphorylated tau, ApoE4 and other agents as redox metals can be aggregated and deposited in intra and extracellular sites on the neuron. Oxidative stress increases all over the brain, particularly in hippocampus and frontal cortex. Aβ-PP [18], PS1, PS2, Tau, ApoE [21,22] and other defensive agents are wrongly processed by proteases and phosphorylation. Genomic vulnerability [23] could result in errors, binding to redox metals in incorrect ways, resulting in Tau hyperphosphorylation, βA peptides, ApoE-macromolecular complexes, which segregate, get insoluble and deposit as amyloid and fibrillar materials leading to senile plaques, neurofibrillary tangles and other protein fibrils [24,25]. In case of depression, the interaction with AD phenotypes trough molecular signaling will accelerate the processes of neuro-degeneration and apoptosis in view of the cortisol cascades, increases of glutamate, Aβ oxidative stress and hippocampal atrophy [26-31] as mentioned before (Figure 1), a very short summary sketch that illustrates the AD –MDD molecular and signaling interaction.

Therapeutic Utility

This interaction model of AD and aging, without any boundaries between either one or other phenotype, is consistent with the clinical observation of elders who have a memory deficit but are not
impaired in their lives. This is a difficult problem for the physicians to make a clear diagnosis as nomination of the disease is definitive only through post-mortem examination, when it is possible to make unsuspected diagnosis [32]. If the elder carries depression [33], aging and memory deficits should strongly raise suspects of symptomless Alzheimer’s disease in course. Particularly on chronic depression, the physicians should look in detail for any sign or symptom of Aging, ACI, MCI and AD vulnerability elders.

Figure 1: Interaction between AD Genomic Vulnerability Longitudinal Cross Talking Spectrum and MDD Genomic Vulnerability Transversal Cross Talking Spectrum

Alzheimer’s disease is a progressive, cumulative and irreversible illness in terms of Amyloid and hyperphosphorylated Tau and macromolecular ApoE complexes deposition on some structures in brain. Oxidative stress starts in the second third of life (30-60 years), with no symptoms. Aging and AD could be the same progressive disorder presenting the phenotypes of molecular and cellular signaling, with the exception that in AD there is genomic vulnerability and, after 60/65 years, cognitive decline appears, progressing to aging cognitive impairment ACI, MCI, and AD.

Major depressive disorder, through transversal cross talking molecular signaling, may interact with AD at any phase in life, once the depressive crisis on any level of Akiskal’s spectrum appears. We see that oxidative stress originates from the Corticoid cascade, elicited by CRF and resulting in an Increase of Ca2+, glutamate, RONS, hyponeurogenesis and consequential hippocampal atrophy. Once hippocampal atrophy liberates CRF increasing glutamate and Ca2+, Oxidative stress may raise, perpetuates the Depression cascades and interfere or interact with the AD cascade accelerating aging and AD, in AD vulnerability elders.

OS – Oxidative stress, RONS – Reactive oxygen and nitrogen species; SAT – Senility Alzheimer Type; ApoE – Apolipoprotein E; PS1, PS2 – Pre-senilin 1, 2; SNAT – Senility no Alzheimer Type; ADGVS –Alzheimer’s Disease genomic vulnerability Spectrum; MDDGVS- Major depressive Disorder Genomic Vulnerability Spectrum; CRF – Corticotropin Release Factor; NFTs – neurofibrillary Tangles; SPs – senile plaques; β-APP – Beta Amyloid Precursor Protein; βA – β-Amyloid Peptide; SNAT – Senility Alzheimer Type; ADGVS – Alzheimer’s Disease genomic vulnerability Spectrum; MDDGVS- Major depressive Disorder Genomic Vulnerability Spectrum; CRF – Corticotropin Release Factor; NFTs – neurofibrillary Tangles; SPs – senile plaques; β-APP – Beta Amyloid Precursor Protein; AD – β-Amyloid Peptide; SNAT- Senility not Alzheimer Type;

that endeavor to avoid aging acceleration, ACI, MCI and AD; and by means of attenuating the Depression cascades in all possible sites of molecular signaling. Contrarily, if the elders are carriers of probable AD, the physicians should look in detail for any sign or symptom in the Depressive spectrum to be treated as prevention of AD recrudescence or as a consequence of dementia. Many other strategies could be executed once one considers for diagnosis and therapy the whole phenotypes of Aging, ACI, MCI and chronic depression. Diagnostic Genetic and neuroimaging studies are consistent with this model as soon asthere is significance of the results; otherwise they could be abolished. Finally we believe that future researches based on this model can contribute to bring more control and prevention for both these neuropsychiatric pathologies.

References


Rodrigues et al. Int J Neurol Neurother 2015, 2:1 • Page 3 of 4


