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

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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 comorbidindication may interact with these AD manifestations - already product of genomic vulnerability - at any stage of the disease. A known example may bemutant 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 severitythat 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 symptomatic 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 paradigmfor 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 asprevious/ 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 knownAlzheimer'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*

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aging,AD may be the normal way of increasing years of life up to death; we would quote it Senility of the Alzheimer Type (SAT), by far the most frequent clinical phenomenology after 85-90 years old people on [1,3,6,7]; and *Senility of No Alzheimer Type (SNAT*), the well least frequent phenotype of aging after 80-90 years old onward [1,6,7]. The following imagined example may clear this proposal: Suppose one has a cohort of a thousand (N=1000) elder people from 65 to 100 years old where no one dies and no new individual enters the group.Consistently with the standard statistics we shouldassignto AD as being 5% at 65 years, more 10/15% at 75, more 20/25% at 85, more,35%-50% at 100 years of age. Obviously, we discount AD incidence percentages from still SNAT elders. Interestingly at this last centenarian age we would have about 80% of the elderly with SAT and only 20% of themwith SNAT! Certainly, if these people could live to 115/120 years of age, we would have much lower frequency of people with SNAT, a percentage unknown currently by obvious reasons. Analogously, as many elder people in reality die before 75-85 years of age, it is impossible to reach to those presented results; and certainly elderly people with SNAT will be in much greater frequency than SAT; not least because SAT may be either a direct or indirect cause of death. This is why the confounding trouble impairs a clear idea in this issue. Moreover, this is because the misunderstanding of MCI and AD diagnosis still leads to clinical and statistical uncertainty in many cases. In practical means: from a community of elders who at 60 years of age do not present any symptoms of AD, at hundred years or more (100+), a mean of 80% of them would present SAT; and only about 20% would be free of AD, presenting SNAT. This means that normal aging incorporates all – clinical, neurobiological and molecular - phenotypes of the illness quoted as Alzheimer´s disease. The genomic vulnerability – the tendency of genes to fail on synthesizing many oxidative stress defense proteins and enzymes [8]- as A β-PP for example – may accelerate oxidative stress and other pathogenic factors; and SAT would manifest earlier (65-70 years of age) than in other not genomic prone individuals. Nevertheless, subject to other AD genetic complexities; to genomic abnormalities as depression, anxiety/stress disorders; andtoa series of environment/ psychosocial factors. Though, many elders die, as mentioned, and we never will know if and when their SNAT will either continue or will turn SAT. This model of natural aging continuity with the progressive deficiency processes [9] leading to cognitive damaging and emotional discontinuity; and depending of the intensity of the "genomic spectrum" of normality/abnormality – DNA and RNA damage [10], enzymatic dysfunctions, metabolic decline, mitochondrial pathology by oxidative stress [11] or some interacting pathogenic illness as depression-is consistent and capable of unifying aging with MCI and AD; and help physicians to diagnosis and therapy, including the mentioned co-morbidities.

In Depression 5-HTTs (serotonin transporters) are some of the defective proteins synthesized by mutant short alleles in the genome of the depressive patient; and there is low serotonin recapture inhibition [12] at the synapse in some brain regions; or the 5-HTT recollection cannot be augmented when in face of a series of psychosocial stresses or diseases. This triggers depression (lowering of life disposition) and CRF/cortisol, glutamate, Ca^{2+}, ROS and RNS (free radicals) to go up from two to seven fold [13]. Free radicals log in cascades of oxidative stress, in case the patient is developing a genomic induced mild cognitive impairment or Alzheimer´s disease;and interact, incorporate and boost it.We can suggest that the molecular signaling on depression is a*"transversal cross-talking signaling"*.This meansthat the various levels of molecular and metabolic processing in function of the individual´s genomic profile - on the Akiskal´s depression spectrum-*in* ***each depressive crisis,*** may interact with Alzheimer´s disease in progress. Furthermore, in the AD spectrum, neuromolecular, cellular, and neurochemical signaling, either being processed in normal or through pathological phenotypes,are continuous, cumulative, and practically irreversible; and in every depressive crisis molecular signaling interaction with AD phenotypes may be a cumulative reinforcing of the pathology. We have considered that Akiskal's depression spectrum scale could be, in analogy, applied to AD in the following sequence: *aging, cognitive ageing disturbance, MCI, sub-thresold AD, clinical AD and terminal AD.* This could be quoted *"progressive longitudinal signaling"* which begin 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 spectrumin 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 useof modern antidepressant drugs 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 – iscontrolledmainly 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 biases, are some of the strongest supporters of the brain energetic metabolism. Asconsequence, 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, ApoEε4 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 andprogressively 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, ApoEε4 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, Ca^{2+}, 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

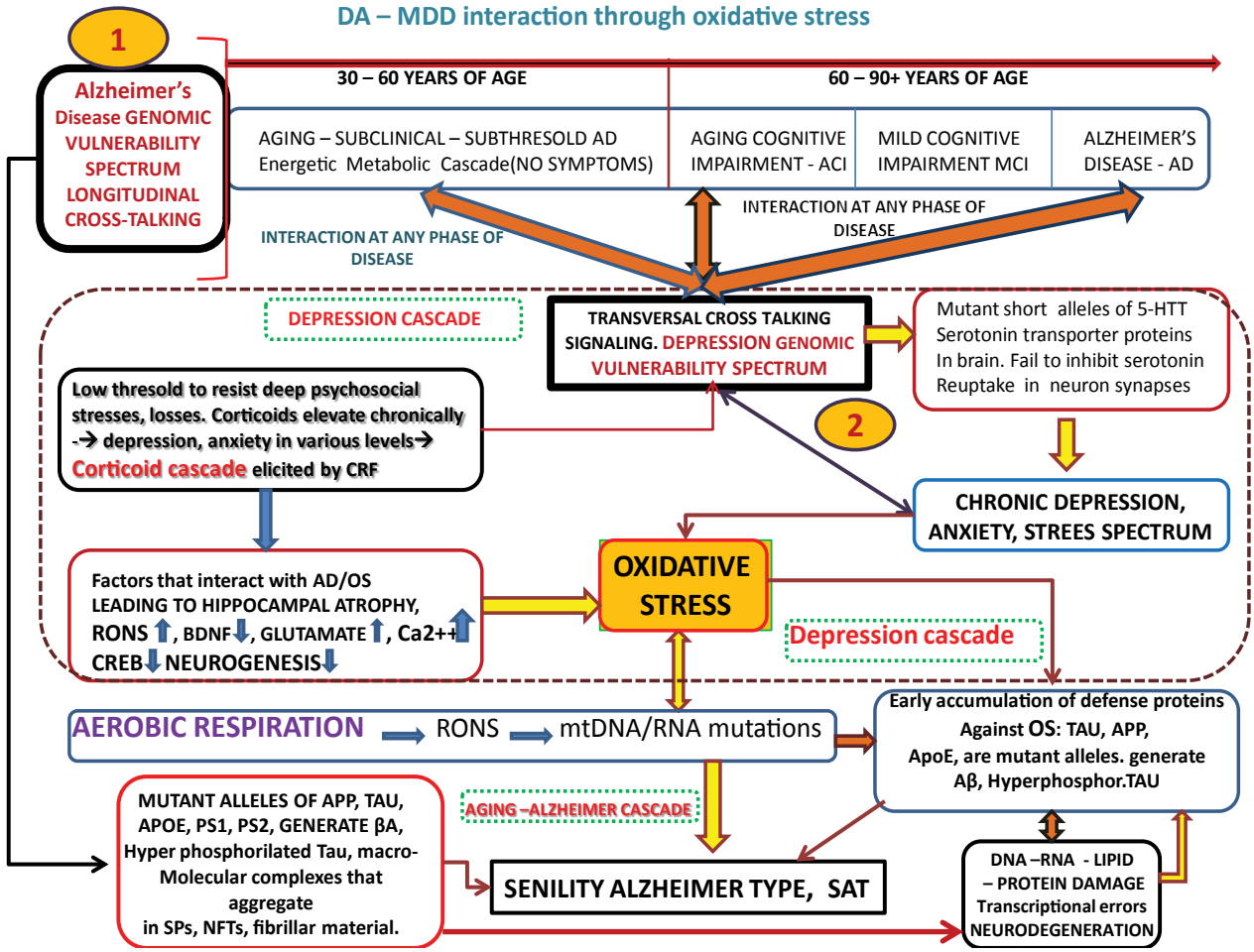

Figure 1: Interaction between AD Genomic Vulnerability Longitudinal Cross Talking Spectrum and MDD Genomic Vulnerability Transversal Cross Talking Spectrum

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, elcited 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 – neurofi-brillary Tangles; SPs – senile plaques; β-APP – Beta Amyloid Precursor Protein; βA – β-Amyloid Peptide; SNAT- Senility not Alzheimer Type;

impaired in their lives. This is a difficult problemfor 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 genomic vulnerability to AD would be of diagnostic and therapeutic importance well before the clinical AD symptoms would appear. Treatment of major depression or any other depressive crisis on the depressive cross-talk spectrum in any phase of life could also be preventive of acceleration forward to AD. Losses, post-traumatic stress disorders, accelerated aging [34], psychosocial and finance decline should be faced in psychotherapy and through a psychiatric psychopharmacological treatment. Cognitive evaluations and exercises also may be preventive in the chronic depression and anxiety stages. Antidepressant, acetylcholinesterase inhibitors, gabaergic, and antagonist glutamatergic drugs could be tried. Anti-oxidants should be ordered on Mediterranean diets by nutritionists. This model is consistent with all these classical and knowntherapeutic measures 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.

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