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Pathogenetic Determination of Selective Vulnerability of Subcellular Neuronal Membranes in Age-Related Dementia

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Abstract: Organic demented states would evolve as patterns of neuronal susceptibility in terms primarily of subcellular or organelle injury. Neurofibrillary tangle formation and neuritic plaque deposition would be associated with amyloidogenesis that progresses largely as a consequence of oxidative stress. Disrupted neuronal circuits might, in real terms, constitute operative mechanistic expression and progression of the demented state that is inherently age-related and that arises as oxidative stress-related phenomena. Interactive pathways of neurodegeneration would perhaps promote the development of constitutional frameworks of Alzheimer-type pathogenesis as individual neuronal and especially as subcellular components, of integral neuronal circuits. Oxidative stress would evolve in terms of a susceptibility of neurons that permits definition of neuronal network dysfunction beyond just individual neuronal cellular pathways. Abnormal synaptogenesis and dendritic dystrophy would arise both in relation to oxidative stress and also to evolving cellular organelle damage that further characterizes the selectivity of neuronal vulnerability. Indeed, it is perhaps in terms especially of ongoing oxidative stress to cellular membrane components that neurons would constitute a primary target in age-related dementia and as Alzheimer-type pathobiology.

Key words: Subcellular, neuronal, membranes, vulnerability, age-related

INTRODUCTION

NEURODEGENERATION–EXPRESSION AND PROGRESSION ARE SELECTIVELY CONTROLLED BY SPECIFIC OPERATIVE FACTORS

A crucial point of concern in age-related dementia is the involvement of genetic factors in the pathogenesis of neurodegenerative disorders characterized by either sporadic or familial occurrence[1]. It would appear that the genetics of neurodegeneration would contribute significantly to the recognized reactive changes characterizing progressive neurodegeneration[2]. Erroneous conversion of signals derived from plastic synaptic changes promote cell cycle activation and cell death pathways[3,4]. A specific context of neurobiology of degeneration would implicate genetic frameworks that allow the operative switching on and off of etiologic mechanisms of progression, as for example via hypoxia or ischemia[5]. Missense mutations in presenilin-1 gene are the most common cause of early onset familial Alzheimer's disease[6].

Situations underlying a variable correlation between genotypic and phenotypic expression[7] might determine not only disease involvement in a particular individual, but also induce progression as an inherited series of predisposing mechanistic pathways such as oxidative stress or possibly amyloid-beta peptide (1-42)[8].

The modes of interaction of genotype with environmental factors would modify susceptibility towards establishment of the active dementing disease process, as, for example, with associated cerebrovascular disease[9]. Hypoperfusion-mediated mitochondrial failure is widely recognized as a pathogenetic factor in Alzheimer's disease[10].

It is not simply hereditary factors that determine whether or not an individual will develop say Huntington's disease, Alzheimer's disease or amyotrophic lateral sclerosis (ALS)[11]. From a clinical and epidemiologic point of view, both hereditary and sporadic forms of a disease such as Alzheimer's or ALS would show increased protein oxidation and lipid peroxidation[12]. Rather, genetics and developmental biology would operatively implicate highly specific mechanisms of proper cell-fate determination and of tissue patterning[13].

The strict operative involvement of a disease category such as Alzheimer's or ALS or Huntington's would be considered pathogenetic largely as a mode of disease predisposition that incorporates also susceptibility to disease progression arising from specific genotypic traits.

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Age-induced alterations in oxidative status may be linked particularly to beta-amyloid deposition[14]. Variations in mitochondrial composition, in particular, may account for selective vulnerability of neurons[15].

Implicated systems of influence in progressive neurodegeneration would perhaps involve genetic disorders ranging from Alzheimer's disease to various dynamic disease characterizations in mode of lesion infliction in the brain or spinal cord. In this manner, altered intracellular glyceraldehyde-3-phosphate dehydrogenase might constitute a common phenotype of neurodegenerative states involving the formation of complexes with neuronal proteins[16]. It is perhaps true that essential characterization of neurodegenerative states as cellular and tissue responses to injury might constitute operatively induced patterns of both inherited and acquired pathogenetic pathways that in some essential way would interactively or correlatively result in relentless progression of the organic demented state. Cerebral atrophy in vascular dementia and Alzheimer disease shows similar volumetric changes and reflects the selective neuronal vulnerability[17].

A relatively few crucial steps would implicate progression of a neurodegenerative process arising as a derived pathway mechanism with etiologic determination and strict characterization of a number of possible pathogenic pathways such as age-related programming of neuron-specific oxidative stress or excitotoxicity[18].

The absence of a key enzyme in a metabolic pathway that gives rise to a subsequent storage disorder such as phenylketonuria would evolve as induced expression and/or progression of states of organic dementia. Such a phenomenon would indicate the genotypic determination of characterized etiologic factors in the evolution of subsequently progressive neurodegenerative states as clinically and pathologically defined.

Alleles at the Nicastrin locus would modify the presenilin-1-deficiency phenotype. Indeed, presenilin-1, presenilin-2 and Nicastrin all form high molecular weight complexes that are necessary for the endoproteolysis of several type 1 transmembrane proteins, including amyloid precursor protein and the Notch receptor, by apparently similar mechanisms[19].

POSSIBLE MODES OF DEVELOPMENTAL PREDISPOSITION TO NEURODEGENERATION AND PRION DISEASE

Accumulation of intermediate filaments as inclusion bodies and as filament aggregates appears a phenomenon common to both skeletal myofibers (as for example with desmin-related myopathies) and central nervous system neurons and glia (as for example with Lewy bodies, Rosenthal fibers, neurofibrillary tangles and Beta-amyloid 4 deposits). Some inclusions and filament aggregates are found in both neurons/glia and skeletal myofibers, whereas others are found only in neurons and glia. Beta-amyloid deposition would involve either the Alzheimer brain or skeletal myofibers as in Inclusion Body Myositis. Selective neuronal vulnerability appears to transcend both brain region and disease state, consistent with common mechanisms of neurodegeneration[20].

Operative systems distinct from simple accumulative deposition would promote amyloidosis; indeed, chaperone function might actually modulate intracellular beta-amyloid metabolism and toxicity in an interactive fashion[21]. Besides accumulation of misfolded or aberrant proteins, synaptic failure, mitochondrial injury together with oxidative and nitrosative stress, dysfunction of the ubiquitin-proteasome system and abnormal axonal and dendritic transport may be implicated[22].

The association of florid beta-amyloid deposition with Prion disease of the central nervous system, as seen especially with the variant form of spongiform encephalopathy (or variant Creutzfeldt-Jakob disease), would implicate bovine spongiform encephalopathy as a pathogenetically distinct disease type. Apparently distinct sporadic and inherited forms of clinical neurodegeneration or myopathy are also central characterizations of various other diseases ranging from Alzheimer's to Parkinson's, ALS, tauopathies and inclusion body-related desminopathies in congenital myopathy. Prion disease might implicate distinct pathogenetic mechanisms of beta-amyloid deposition that also prove particularly significant as deposition of senile plaques and as neurofibrillary tangles. Congophilic angiopathy evolves in relation to both Alzheimer's disease and increasingly old age in a manner that tends to spare the occipital region of the brain in terms of senile plaque deposition, neurofibrillary tangle formation and cortical atrophy.

Lewy bodies are reactive for alpha-synuclein in the substantia nigral neurons of patients with Parkinson's disease. They occur also diffusely in cerebral cortical neurons and in glial cells of patients with Lewy Body Disease.

This Lewy body variant Alzheimer's disease would arise as variability in genotypic and phenotype determination of the demented state[23]. Mitochondrial cascade pathways, neuronal aneuploidy and programmed cell death would promote amyloidogenesis and reactive oxidative stress[24].

Chaperone proteins, including Torsin A and heat shock proteins, would play a specific role in cellular responses to neurodegenerative inclusions[25].

Both oxidative stress and abnormal mitotic signaling appear involved in propagating disease pathogenesis[26].

Even the inclusion body myopathies associated with both normal and abnormal desmin and actin molecules would implicate pathogenetic progression that is expressed in both neuronal/glial and myofiber pathology. In this regard, also, the beta-site amyloid precursor protein-cleaving enzyme, beta secretase, is a prerequisite for the generation of beta-amyloid peptides that give rise to cerebrovascular and parenchymal beta-amyloid deposits in Alzheimer brains. This enzyme is expressed in astrocytes in a stimulus-dependent manner in cases of organic dementia[27].

The apparently highly diverse specific etiologic agents affecting either the central nervous system or skeletal musculature might operate simply as derived properties of a fundamental, constitutional response to cell injury. Membrane lipid peroxidation and oxidative modification of receptors, ion transporters and channels, signal transduction and cytoskeletal proteins are characteristic of neurodegenerative states[28].

Strict considerations of specific etiologic agents giving rise to Alzheimer's disease or to Prion disease[29]or to Inclusion Body Myositis or myopathy[30] would exhibit evolving susceptibility with features shared with other modified forms of neurodegeneration such as Multi-system disease. Indeed, pathogenetic diversity might operate within systems of modified expression and progression of pathologic involvement. Prion disease would necessarily incorporate interactions between the Prion particle and the neuron that are expressed and that variably progress. Even Alzheimer-type changes affecting nondemented senile subjects, as well as patients with Down's syndrome over 40 years of age, would implicate constitutional attributes arising as operative factors involving especially microglial reactivity and microgliosis[31]. Such constitutional attributes could potentially modify pathologic involvement both as a defined sporadic disorder and as a familial trait.

This would implicate also disorders such as corticobasal degeneration[32]. Distinction of Alzheimer's disease from just Alzheimer-type changes in senile patients would specifically involve constitutional attributes that modify evolving pathologic progression as initially etiologically determined pathway mechanisms. Constitutional processes appear significantly modified by increasingly old age and also by certain genetic disorders. In Down's syndrome, for example, estrogen might play a protective role that modifies the neurodegenerative and cognitive decline. Estrogen might act via endogenous growth factors[33]. Also, estrogen withdrawal would potentiate the phenotype associated with Amyloid precursor protein overexpression[34]. Active constitutional systems would determine the state and degree of functionality of organs such as brain and skeletal muscle. A simple pathway of etiologic derivation as specific lesions would not fully account for all expressed manifestations of Alzheimer disease patients. It is perhaps in this sense that the term "neurodegeneration" would characterize a potentially highly variable range of constitutional factors determining not only the severity of the dementia but also whether the patient will develop Alzheimer's disease in the first place, as an organic demented state.

Constitutional attributes would act as primary factors in the development of various neurodegenerative disorders that occur sporadically but are otherwise a familial attribute. Such a phenomenon would imply accumulative genetic injury within families as one specific genotypic characterization of disease expression. Indeed, Alzheimer's disease and other states of neurodegeneration or myopathy, including Inclusion Body Myositis[35], would arise as constitutional disorders that subsequently implicate increased neuronal susceptibility to injury such as oxidative stress.

Prion disease might arise as individual mechanisms of expression and progression of a disease state that is subsequently predominantly inherited or else occurs as a predominantly sporadic disorder.

Impaired glucose and mitochondrial function, as induced by lesions at a genetic level, might contribute significantly to the pathology of various brain disorders and dysfunctional states ranging from Alzheimer's to Parkinson's and schizophrenia[36]. Highly variable constitutional attributes would implicate susceptibility to specific putative etiologic agents that actively promote progression of neurodegenerative lesions.

ASSOCIATED SPECIFIC MORPHOLOGIC LESIONS IN ALZHEIMER'S DISEASE PROMOTING OPERATIVE FACTORS

Within a clinicopathologic spectrum of Alzheimer-type changes there would develop susceptibility patterns promoting accumulation of neurofibrillary tangles in disease progression.

Neurofibrillary tangle formation would constitute a central series of pathologic phenomena in neurodegenerative disorders that directly modify morphologic lesions and the organic demented state. Even the senile dementia with tangles seen in very old subjects, particularly females, would be consistent with neurofibrillary tangles correlated pathogenetically with advancing age. A principal attribute in neurodegeneration

that is related to advancing age might very well implicate multiple pathogenetic agents. Classic Alzheimer's disease would evolve in terms of various pathogenetic agents producing neurofibrillary tangles and also in terms of predisposition to neuritic plaque deposition and interactions that are specifically amyloidogenic[37].

Beta-amyloid 42, a proteolytic breakdown product of the large amyloid precursor protein, would play an early critical role in Alzheimer disease pathogenesis[2], related for example to possible oxidation of cytoplasmic RNA[38].

Frameworks of Classic Alzheimer disease progression concurrent with aging might operate as variable pathologic severity or degree of deposition of Lewy bodies, subcortical involvement of cerebral white matter, apoE type participation and cortical atrophy. Development of neuropil threads, argyrophilic grains, Hirano bodies and granulovacuolar inclusions would constitute pathogenetic modes of association in evolving expression and progression of the Alzheimer brain process.

Anionic surfaces presenting as micelles or vesicles would nucleate tau fibrillization, with fatty acid inducing action[39].

Alzheimer's disease as an essential variability in degree of cortical atrophy, or as more localized or circumscribed lobar types of atrophy, might implicate a distinct heterogeneity of expression of morphologic lesions in the brain as seen especially in the hippocampus and allocortex. Such a phenomenon might involve in particular a site-specific process in the initiation of neurofibrillary tangle formation in Alzheimer's disease.

Senile dementia with tangles would constitute complex morphologic evolution of neurodegenerative events. Innumerable constitutional factors would promote susceptibility to development of the various morphologic lesions in Classic Alzheimer's disease.

A decrease in brain-derived neurotrophic factor synthesis may promote selective neuronal cell death in the hippocampus, cortex and basal forebrain cholinergic systems in Alzheimer's disease[40].

Association of neurofibrillary tangle formation with the development of neuritic plaques, neuropil threads, ischemic type changes and Beta-amyloid deposition, would possibly help strictly characterize virtual pathogenesis that promotes actively inducing lesions. Neurofibrillary tangles as interactive expression and progression pathways in neurodegeneration would predispose to brain atrophy that is linked pathogenetically rather than etiologically to aging. A strict framework of common associations of main pathologic lesions as seen in Classic Alzheimer's disease would include perhaps neuropil threads and argyrophilic grains as different stages in development of neurofibrillary tangles[41]. Integral constitutional systems of upset that affect different neuronal subcompartments as expressed morphologic lesions would subsequently promote brain atrophy in Alzheimer patients. Intracellular beta-amyloid accumulation in Alzheimer brains would induce biochemical and pathologic changes in priming neurons to further forms of injury[42].

A relationship appears to exist between caveolin-1 expression levels and a dysregulation of cholesterol homeostasis at the neuronal plasma membrane[43]. Cytochrome C release from mitochondria may promote oligomerization of amyloid beta and alpha-synuclein; the apoptosis cascade is thus activated as a result of interactions of misfolded synaptic proteins[44].

NEURODEGENERATION AS INHERENTLY HEIGHTENED SUSCEPTIBILITY TO INJURIOUS AGENTS

Frontotemporal dementia with Parkinsonism linked to chromosome 17 (FTDP-17) would involve relative sparing, grossly and microscopically, of the hippocampus, even though cortical atrophy generally affects the temporal lobe. The relative paucity of neuronal cell loss, of gliosis and the relative absence of neurofibrillary tangles in the hippocampus, would be suggestive of distinctive pathways of neurodegeneration in this disorder. Particularly in view of subcortical and brain stem involvement in patients with FTDP-17, a global process of neurofilament/tau specificity would operatively spare the hippocampus. An added spectrum of clinical features and pattern distribution of lesions in the individual case with FTDP-17 would further implicate an important role for various constitutional attributes in patient disease progression.

Increased tau proteolysis would develop in conjunction with increased neuronal apoptosis and in the absence of accumulated insoluble tau deposits[45].

Neurodegeneration would characterize strict topology of lesions related to either earlier stages of the disease, or to pathological involvement of essential neuronal subcompartments that operate individually within integral neuronal circuits. Somatic control region mitochondrial DNA mutations may account for some of the mitochondrial defects in Alzheimer's disease[46]. It is perhaps in such defining terms that the familial attributes of FTDP-17 would involve neurons as integral neuronal circuits.

Altered handling of tau protein as pathologic processes of aggregation might simply be an expression of a brain aging process that subsequently heightens susceptibility to further neurodegenerative progression[47].

Lysosomal dysfunction might trigger the parallel formation of meganeurites and tangles in regionally

selective groups of neurons[48]. Lysosomal membranes co-localize gamma secretase activity with presenilin-1, amyloid precursor protein and Nicastrin[49].

FTDP-17 would somewhat parallel cognitive disorders such as Huntington's disease that arise as inherited organic dementia with age-related disease expression[50]. The effect of Beta-amyloid would appear, for example, potentiated by concurrent exposure to inflammatory cytokines as derived from activated glial cells, to induce neurotoxicity-such cytokines include Interleukin-1 that in turn would induce expression of other cytokines such as Interleukin 6[51,52].

In general, one might appreciate existing metabolic or cell biologic defects[53] inherited, not as neurodegenerative cascades, but as mechanisms that directly lead to dementia through constitutional pathogenetic systems determining expression and progression of disease[54].

Constitutional pathogenesis in several cases of dementia appears operative beyond a simple cause-effect relationship. Altered patterns of acidic fibroblast growth factor immunoreactivity possibly mark selective neuronal vulnerability in Alzheimer's disease in terms of protection against glutamate excitotoxicity[55].

It is particularly in terms of a predisposition to neurodegeneration that hereditary systems would predispose to a disorder such as FTDP-17 as active neuronal injury[56].

Neurodegeneration would be distinctive as a pathobiology arising primarily from heightened neuronal susceptibility involving cellular and subcellular membrane/organelle injury. Increased neuronal susceptibility to mitochondrial injury would promote different pathways of apoptotic cell death resulting from oxidative stress[57].

In spite of a pathogenesis in neuronal cell death, neurodegeneration would specifically evolve largely as differential patterns of susceptibility to such neuronal cell death.

Interactive and correlative systems of susceptibility involving phenotypic and genotypic characterization of organic demented states might be expressed as evolving neuronal injury in an age-related fashion. In this manner, systems such as oxidative stress that are directly implicated in many processes of aging, would perhaps correlate with selective susceptibility of neurons in organic dementia and differentially evolve as mechanisms of pathogenesis.

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