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Reaction to Injury Promotes Neuronal Dropout in Alzheimer's Disease

Lawrence M. Agius
Department of Pathology, St Luke's Hospital,
Gwardamangia Medical School, University of Malta, Msida, Malta Europe

Abstract: Set patterns of evolution of the Alzheimer's disease process might follow systems of reactivity in response to injury affecting multiple neuronal suborganelles. This may be conducive to the creation of programmed events as individual cell loss or neuronal dropout. The neuronal plasmalemma and other membranous cell components, would lead to the generation of progressive cascade-like events in neuronal depletion and brain atrophy. Selective vulnerability of neurons might specifically implicate pathobiologic processes that affect responsive elements in progression of the injury. Such injury appears based on integrative pathways induced especially by trophic factor insufficiency and vascular hypoperfusion. Alzheimer's disease appears to evolve as compromised recoverability of neurons that further delineate susceptibility patterns of neuronal subsets. Indeed, the neuronal pathobiology in Alzheimer's disease would center on aberrant modes of reactivity to a host of potential injurious agents that subsequently may evolve as programmed neuronal cell loss. Such cell loss would primarily arise on an individual neuronal cell basis and subsequently develop into aggregate loss of network connectivity.

Key words: Neuronal dropout, reaction, alzheimer's

INTORDUCTION

Selective neuronal susceptibility as integral network disruption in alzheimer's disease: Primary selective vulnerability of neurons would involve modes of neuronal reactivity as regional and specific agents of injury. It is with regard to neuronal reactivity rather than simply to neuronal viability that selective vulnerability would implicate injury due to hypoxia, toxicity or even reperfusion injury. Relatively constant levels of selected receptor subtypes may represent a compensatory up-regulation of these receptors subunits in surviving neurons. Even in terminal stages of Alzheimer's disease, the brain attempts to maintain a balance in excitatory and inhibitory tone as reflected in glutamate and GABA receptor subunits[1].

There would develop set circumstances within neurons that are regional in terms of how individual neurons would thus become reactive. It has been postulated for example that a defective blood brain barrier results in neuronal expression of immunoglobulins and a possible autoimmune response that induces neuronal cell death[2]. Select anatomical or physiological subsets of neurons may possess specific receptor subtype, linked to susceptibility reactivity involving pathobiologic dynamics that are not solely based on functional-structural interactions[3].

Involvement of the cholinergic system in the Alzheimer brain and a predilection for amyloid deposition in neuritic plaques and walls of blood vessels might progress as postsynaptic receptor injury that induces both neuronal and blood vascular-reactive patterns. β-amyloid protofibrils possess a core structure that is resistant to hydrogen exchange; this may promote neuronal dysfunction and cell loss in Alzheimer's disease[4].

There develops a particular susceptibility to neuronal loss with increasing age of the patient as an Alzheimer process involving constitutionally or genetically predetermined neuronal injury[5] as with abnormal nuclear signaling interfering with PSI/epsilon-secretase cleavage and leading to production of transcriptionally active intracellular fragments[6]. Abnormal neuronal receptivity may be responsible for a series of reactions that progressively injure neuronal subsets. These may include ubiquitin-proteasomal system, oxidative stress and free radical formation, impaired bioenergetics and mitochondrial dysfunction and neuroinflammation[7]. Neurons as acquired environmental influences would recharacterize neuronal reactivity relative to increasing age of the individual[8].

Neuronal receptivity implicates impaired reactivity on the part of subset neurons that reflects a postmitotidec progression and transformation of neuronal constitutional

Corresponding Author: Lawrence M. Agius, Department of Pathology, St Luke's Hospital, Gwardamangia, University of Malta Medical School, Msida, Malta Europe Tel: +356 21451752/+356 25951663 Fax: +356 21 224286

activities and abnormal blood supply and trophic factor response. Also, the mechanism of cell loss (a cell-cycle-induced death) and the rate of cell loss (a slow atrophy over months) would correlate with the cognitive decline in Alzheimer's disease[9]. Neurons are selectively classifiable in terms of a large number of attributes, particularly in relation to cell size and axonal length, thus effecting a neuropathophysiology of Alzheimer's as an aging deterioration of network projections and as evidenced by cholinergic predisposition to further network disease progression[10], this may include selective loss of α-4 β-2 nicotonic acetylcholine receptors[11] .

Cell receptors reflect responsiveness of cells implicating dynamic ligand shifts between the extracellular and intracellular compartments. Neurons in Alzheimer's disease involve modes of neuronal response to such signals as atrophy or decreased trophic effect and in a context of a whole host of toxic exposures and of hypoxia. Modes of neuronal death in Alzheimer's disease would not involve just apoptosis or denervation or even mechanistic spread of the disease process from the hippocampus. Neuronal dysfunctionality would delineate progression of neuronal injury as cell loss in terms of failed receptivity and of neuronal dystrophy. Trophic insufficiency implicates modes of neuronal injury that lead to disease progression as a network pathobiology. Alterations possibly affect expression of specific NMDA receptor subunits with increasing progression of the Alzheimer pathology, thus contributing to neuronal vulnerability[12]. Network dysfunction of neurons may possibly promote neuronal cell loss due to induced transformed intracellular events, thus leading to membrane-anchored proteolysis or even apoptosis.

Cytoarchitecture of neurons constitutes pathobiologic response to injury as neurofibrillary tangle formation and as inclusions in further enhancing neuronal progression of the injury. Neurons constitute targets of an injury that bridges vascular supply, trophic insufficiency and amyloidogenesis in predisposing to neuronal cell loss. Vascularity of the cerebrum might induce active neuronal cell loss due to oxygen free radicals and excitotoxicity affecting neuronal networks and especially cell suborganelles. Membrane proteolysis as protein-protein interactions would implicate synaptic junctions as individual neurons react to injury affecting primarily neuronal networks. Schemes of evolving neuronal injury may self-progress as targeted pathways involving increased susceptibility leading to individual cell loss.

Formation of nitric oxide by astrocytes may contribute to mitochondrial impairment in promoting neuronal cell loss[13]. Apoptotic pathways might evolve as injury arising from induced toxicity or trophic factor insufficiency. Decreased amounts of Nerve Growth Factor (NGF) at the level of Basal Forebrain Cholinergic Neurons (BFCN) cell bodies result mainly from failed retrograde transport rather than from impaired synthesis, binding or expression of NGF receptors in the BFCN terminals[14].

Amyloidogenesis involves neuronal toxicity and vascular compromise leading to a pathobiology of the individual neuron within integral neuronal networks[15].

The actual phenomenon of brain atrophy is one primarily of relentless progression regardless of whether disease onset is presenile or senile. Familial characterization of early onset patients might primarily reflect a disease process targeting whole integral subsets rather than just individual cells[16]. Cellular involvement may selectively target groups of neurons in the cerebrum from initial stages of the disease. Cyclin-dependent kinase 5 is deregulated in Alzheimer brains and may contribute to its pathogenesis due to neurotoxic action[17]. Actual tissue loss as brain atrophy may implicate decreased viability of cells due to vascular compromise and impaired recoverability of neurons injured by a potentially varied host of possible insults. The actual cellular response to injury might determine targeting dynamics as membranous cell organelle disruption or as excessive proteolysis.

Reactivity patterns of injury to neuronal membrane organelles would refer to lytic events enhancing protein-protein interaction. Cell loss would be an end-result of microglial phagocytosis of the membranous debris in terms of neurofibrillary degeneration in neuritic plaques. Alzheimer disease pathogenesis refers to the progressive onset of a demented state that disrupts synaptic connectivity[18]. Such a process might, for example, possibly arise as a primary axonal pathology that subsequently spreads both proximally and distally to include the neuronal cell body and synapse. p-JNK and cdk 5 colocalize in cell bodies and neurites; a cellular link between the cdk5 system and the stress kinase JNK and p38 pathways may provide an alternative pathway to neuronal death[19].

On the other hand, a strictly synaptic pathobiology might also involve cell dendrites and axonal terminal as an evolving disease process. A variability of expression may affect a degree of injury to both dendrites and axonal terminals that subsequently injures synaptic components. A primarily dementing disorder of Alzheimer type would induce neuronal cell loss subsequent to synaptic involution that specifically accompanies brain atrophy. Such neuronal cell loss might give rise to various degenerative states inducing neurofilament tangle formation and impaired neurotransmission. An imbalance in availability of chromogranins may lead to impaired neurotransmission due to reduced functioning of dense core vesicles and loss of presynaptic proteins involved in exocytosis[20].

Lack of trophic factor arising from insufficient vascular blood supply might promote an axonal dying back and atrophy of the cell body. Dendritic tree and axonal co-participation in an overall dying back phenomenon might implicate an atrophy of the cell body that promotes synaptic loss. The brain atrophy may implicate a synaptic dysfunction and also axonal and dendritic loss of individual neurons.

Selective neuritic involvement leads to subsequent post-mature plaque formation of evolved disease in alzheimer's: Alzheimer's disease, as an essential neuronal endpoint is a process progressing as extension of neurite plaque confines into the surrounding neuropil. Specific dimensions of the individual neuritic plaque may progress as parameters of a neuronal dropout phenomenon affecting cerebral cortex or hippocampus. Dimensions of neuritic plaque expansion may arise as parameters of the neuritic arborizations of individual neurons. The neuritic plaque evolves concurrent with neurofibrillary tangle formation as an Alzheimer process of co-occurrence of various lesions. Deafferentation and intrinsic neurofibrillary degeneration possibly contribute to dendritic loss concurrent with disruption of the neuronal cytoskeleton, axonal degeneration and loss of presynaptic elements[21]. Oxidative stress may modulate the metabotropic glutamate system, cell cycle regulation in postmitotic neurons and control GSK-3β activity and presenilin integrity. These mechanisms may centrally affect mitochondrial membrane permeability through trophic factors, mitochondrial energy supply and the Bcl-2 family members[22].

Only insofar as it is possible to classify neuritic plaques as mature or burntout and also as recognizable lesions even in early disease stages can one invoke accompanying cell elements such as microglia and astrocytes in the programmed neuronal cell loss and neuritic dystrophy. A global neuritic involvement would account for a neuritic dystrophy that evolves concurrently with individual neuronal cell loss in the Alzheimer brain. Senile-type changes that influence progression of such cell loss would account for also a neuritic dystrophy that progresses as the senile plaques mature. Selective neuronal loss may activate caspases and execute apoptosis and induce tau proteolysis with neurofibrillary tangle formation[23].

It appears possible to delineate a dystrophy that initially marks out a number of neuronal subsets in disease evolution, thus progressing as the post-mitotic neuritic plaque that includes an amyloid core. Scaffold proteins such as caveolin and JNK-interacting protein may fail to integrate signaling pathways and correlate with accumulation of misfolded β amyloid and α-synuclein with synaptic loss[24].

Individual neuronal dropout as eventual aggregate neuronal loss in progression of the alzheimer disease process: Alzheimer's disease implicates not only transformational events in amyloid deposition but also individual neuronal cell loss specifically related to the amyloidogenesis. Such amyloidogenesis induces abnormal trophic influences arising as a neuronal cell death program. Chronic brain hypoperfusion in particular may mimic cognitive impairment experimentally. Hippocampal dysfunction may result from shear stress induced by nitric oxide release from endothelium in maintaining homeostasis of local blood flow[25].

Transformational events affecting neuronal cell loss might activate initial neurofibrillary tangle formation and induce vascular and neuritic plaque damage with amyloid deposition. Chronic brain hypoperfusion per se is linked to risk factors for Alzheimer disease[26]. The neuritic plaque is an enhanced pathway of amyloid deposition leading to a concurrent loss of neurons. Dropout of individual cell units evolves as Alzheimer disease progresses. Deposition of amyloid is centered on events critically implicated in neuritic plaque generation. A neuronal dropout phenomenon is both transformational and progressive as brain atrophy in Alzheimer's disease. Aberrant hyperphosphorylation and aggregation of tau protein accompany synaptic loss and dying back of axons and may contribute to abnormal transport of vesicles and cell organelles[27].

Manifestations of neuronal pathology in Alzheimer's are simply adaptive modes of response to a putative agent in causation of the disease process arising from and culminating in, individual neuronal cell loss[28].

In this manner, β-amyloid would trigger caspase activation, with subsequent cleavage of tau and neurofibrillary tangle formation[29]. Such a process would induce subsequent transformation to whole-aggregate loss of such neurons.

The programming of targeted non expression by neuronal cells in alzheimer brain atrophy: Programmed cell death as a targeted neuronal dropout phenomenon evolves during the course of Alzheimer disease pathogenesis. This may implicate not simply apoptosis but a programming profile of responses to a variety of neuronal insults. Alzheimer's disease starts and progresses as a stereotyped phenomenon with well-defined pathologic effects. The brain atrophy is a process targeting the neuronal constitutive expression of various

membrane epitopes or receptors. β-amyloid protein in compact fibrillar plaques can induce an innate immune response that provokes neuroinflammation, neuronal cell loss and further deposition of β-amyloid [30]. An overall programmed targeting inhibits neuronal response, culminating eventually in brain atrophy.

Constitutive variability of response on the part of neurons to various insults range from β-amyloid toxicity to ionic fluxes to oxidative stress. These might implicate evolutionary pathways linked, on the one hand, to fundamental pathobiology of the Alzheimer disease process and, on the other, to cascade-like disease events responsible for neuronal cell dropout and as brain atrophy. An initial event in Alzheimer disease pathogenesis implicates not only cascade-like progression but also injury as oxidative stress that modulates programmed cell death through the action of cysteine proteases and protein kinase B (Akt), with subsequent membrane phosphatidylserine exposure and DNA degradation[31].

Cellular injury is only one facet of a targeting of responsive elements resulting in loss of receptivity and of epitope presentation on neuronal cell membranes. Various systems of cellular progression involving induced response to such injury might implicate a neuropathology in Alzheimer's simply as a progressive injury to plasmalemmal, proteolytic and other systems of cellular synthesis and degradation. Accumulation of misfolded β-amyloid and α-synuclein oligomers in the mitochondrial membrane might result in release of cytochrome C and subsequent onset of apoptosis. Plasmalemmal damage may also result from translocation of protofibrils[32].

Amyloidogenesis is a fundamental expression of such targeted responses that evolve largely as dynamic processes of influence in cell injury and recoverability. Fibrillar β-amyloid induces neuritic dystrophy with marked loss of synaptophysin immunoreactivity[33].

Injurious agents initially determine the outcome of a disease process such as Alzheimer's in terms of a neuronal cell dropout phenomenon. Targeted expression of neurons as both modulated response and also as actively suppressed recoverability involving cascade series of programmed events would promote neuronal cell loss affecting extensive areas of the cerebral cortex[34].

Alternatively controlled desuppression and suppression in disease pathogenesis would culminate in loss of normal expression of various suborganelle functional units ranging from bilipid membrane assymmetry[35] to associated protein-protein interactions and genomic involvement. Calpains, calcium-dependent cysteine proteases, may be affected; these modulate enzymes involved as signaling molecules and also in cytoskeletal rearrangement and cell motility, signal transduction, vesicular trafficking and stabilization of neuronal structure[36].

Loss of gene expression appears to constitute a predilected disease activity as targeting events in neurodegeneration that result in initial shrinkage of the neuronal cell body. Involved participation of various lesions in the same targeted neurons would progress as widespread neuronal loss. In this manner, the cholinergic lesion that is present in early stages of the disease may influence progression through interactions with amyloidogenesis, tau phosphorylation and neuroplasticity[37].

The nonexpression of certain dynamic processes in synthesis would result in a process of cumulative effect promoting neuronal cell death. The deposition of β-amyloid would involve expressed nonviability of neurons affecting also smooth vascular myofibers. Alzheimer's disease would evolve as an integral process of neuronal injury possibly involving different pathways of initial development. An expressed neuronal phenotype would contribute to disease progression affecting neuronal receptivity that is linked ultimately to selective vulnerability of cells as predetermined in embryologic development through neurotrophin expression[38]. Activation of the c-Jun N-terminal kinase pathway is critical for naturally securing neuronal cell death during brain development and may be implicated in Alzheimer's disease[39].

Possible progression as a targeted responsiveness in further cascade-like events possibly transforms individual cell loss to significant brain atrophy, as along neuroinflammatory pathways[40]. Genes implicated in early onset autosomal-dominant Alzheimer disease are the amyloid precursor protein, the presenilin-1 and presenilin-2 genes; other genetic and environmental factors may modulate disease expression with variability even among family members with the same mutation[41].

The neuronal cell membrane in particular appears quantitatively implicated as an evolved process that arises as neuronal cell pathobiology. Even if, in such a sense, nonexpression of membrane epitopes results from gene silencing, the neurodegeneration in Alzheimer's disease would prove actively progressive in terms of a neuronal pathology ranging from neuritic plaques to neurofibrillary tangles. In this sense, disease pathogenesis might perhaps implicate patterned variability of response ranging from membrane proteolysis to accelerated degradation and induced protein-protein

interactions affecting various neuronal subsets, but culminating in transformation of an initially individual neuronal dropout phenomenon.

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