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Beyond Neuronal Cell Lossin Tissue Atrophy of Alzheimer Type

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Abstract: Alzheimer disorders of neuritogenesis and of senile plaque formation are progressive in terms of a developmental predetermining series of steps in evolution of amyloidogenesis and of neuronal cell depletion and loss. Tissue atrophy of the cerebral cortex and white matter appear both integral aspects of a disease process that evolves to implicate microcirculatory and vascular wall pathology or impermeability. The extracellular dimensions of the senile plaque appear exquisitely sensitive to the conditioning and transforming influences of pathology of Alzheimer type. Neurofibrillary tangles and congophilic angiopathy and also the various other manifestations of Alzheimer brain atrophy include a particular association with neuritic dystrophy and dysfunctionality of synapses and of neuronal circuits. It might be particularly significant to recognize the Alzheimer disease process as one that inherently arises in consequence to a variety of associative factors that secondarily determine developmental progression of neuronal cell loss and of tissue atrophy. A central process of apoptosis as transformed dynamics of cell loss and of altered attributes of otherwise active maintenance of cell metabolic and physiologic pathways might account for a depletion that is genetically programmed but predominantly associated with acquired associative events of progression.

Key words: Neuronal cell, Lossin tissue, Alzheimer

BEYOND A SIMPLE PROCESS OF NEURONAL CELL DEPLETION IN NEURODEGENERATION

A predilected targeting of specific neuronal subpopulations would allow for recategorization of clinical features in terms of pathogenesis and presumed etiology of various neurodegenerative disorders. A distinction between Alzheimer's disease from, say, amyotrophic lateral sclerosis would appear essential as an aspect of the biology of the neurodegenerative process that evolves largely in terms of a specific etiologic lesion in one or other disorder. Targeted gene therapy of Nerve Growth Factor appears a potential method for reducing neuronal cell loss[1].

Amyotrophic lateral sclerosis would arise and develop in a manner that is characteristic of a classic model of the disease. However, aspects of neurodegenerative disorders in general contrast with specific distinguishing features of diseases such as viral encephalitis, cerebrovascular disorders and trauma in a manner that is often referable to CNS anatomic sites of involvement by disease.

However, Alzheimer's disease would represent a characterization of a process showing specific anatomic involvement, of clinical features of an integral syndrome and of aspects of a presumed pathogenesis such as synaptic loss or trophic factor insufficiency.

Senile versus nonsenile features of brain atrophy would involve morphology and even molecular features that help distinguish pathologic involvement in Alzheimer's disease. Disease involvement in clinical dementia appears however a process that goes beyond just morphologic aspects such as neurofibrillary tangles or senile plaques, or beyond molecular pathogenesis as constituted by tau neurofibrillary tangles or of Beta amyloid deposition. An integral progression of disease that implicates the individual patient in large part appears to involve genetic determinant influences in a recognizable mode pattern. Impairment of neuronal metabolism and of neuronal viability appears to more clearly distinguish Alzheimer's disease from, say, amyotrophic lateral sclerosis.

Hence, organic dementias would be grouped together to be distinguished individually and as a group from other neuronal disorders such as HIV AIDS-dementia Complex[2] and multi-infarct dementia.

Hereditary or sporadic acquisition of a disorder that is reflected in depletion of neuronal subpopulations would implicate the development of characteristic disease modes or patterns of progression. Neurodegeneration is essentially a developmental process of involvement that progresses in relative proportion to patterns of influence exerted by systems of circulatory insufficiency and senility.

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It also develops in association with other processes such as selective susceptibility of impaired neuronal viability and of genetic predisposing influences and beta-amyloidosis.

Synaptic loss would progress in terms of lack of trophic factors and of beta-amyloid deposition as a strict causal factor in primary neurodegeneration. Alzheimer's disease would implicate an association of involved patterns of neurodegeneration that transcend simple cerebral cortical pathology.

Organic dementia would constitute an integral effect of various lesions affecting viability of neurons in a patterned series of neurodegenerative steps in evolution of the clinical demented state.

Simple patterns of association that involve viability or nonviability of neurons would not distinguish affected neurons simply on the basis of distribution or of morphology but rather as units that are susceptible to specific patterns of disease progression.

Alzheimer's disease would develop etiologically via specific pathogenic pathways of direct cause and effect. Associations of influence that participate in the development or nondevelopment of processes of neuronal nonviability would depend on how genetic attributes in fact react to exposure to and depletion of influence.

Development of the demented state appears to exhibit central attributes of depletion type. Indeed, neurodegeneration would be contrary to a basic process of development of neuronal cell death as a primary cause of cerebral cortical atrophy that presents as senile dementia. In perhaps an extended view of how Alzheimer's disease does arise and progress one might have to consider systems of influence that would prevent a damaged neuron from dying due to a phenomenon of tissue depletion.

Progressive neuronal loss of viability would be associated with attempts at prevention of neuronal cell death atrophy or focal synaptic losses[3].

NEURONAL NONVIABILITY OF INHERITED OR SPORADIC OCCURRENCE

Genetic disease occurrence may at times manifest as apparently sporadic disorders. Alzheimer's disease appears a constitutionally determined disorder but one that subsequently often implicates also acquired sporadic systems of progression. Alzheimer's disease appears a constitutional adaptation of neurons in a manner that develops often in terms of a sporadic phenomenon of progressive non-viability of the neurons. It is in this sense that it is often difficult to qualitatively distinguish brain atrophy due to simple senility from atrophy of Alzheimer type.

Constitutional factors determining fate of neuronal subpopulations would implicate a patterned mode of progression and distribution that actually arise in terms of opportunities of associative effect of a sporadic nature. Cell cycle events appear to induce neuronal cell death as a slow atrophy at all stages of the Alzheimer disease process[4]. These would paradoxically determine not only the clinical occurrence of the Alzheimer process in that patient but also distinguish senile brain atrophy from Alzheimer disease in purely qualitative terms.

Disease involvement would be resolved in terms of degree of progression of various neuronally determined processes[5] that go beyond simple quantitative attributes of the brain atrophy. The neurodegeneration of Alzheimer's type is one that arises purely from quantitative factors of influence that operate developmentally in the usually sporadic occurrence of an atrophic brain process.

Alzheimer's disease is a disorder that is relentlessly progressive in terms of aspects of biologic involvement of neurons that transform viability to attempts at preservation of such cellular viability. A whole host of attempts at preservation of neuronal viability would progress in an essentially aberrant manner to finally resolve outcome of neuronal depletion and cell death. Hippocampal atrophy appears a result of neuron loss[6].

In this sense, Alzheimer's disease constitutes an attempt at neuronal survival that is manifested clinically through a series of aberrantly developed pathways of association and influence acting on subsets of neurons distributed regionally and globally, in response particularly to decreased neurotrophic effect[7].

A PRIMARY PATHWAY OF NEURODEGENERATION THAT IS SECONDARY TO SPORADIC FORMS OF INFLUENCE

Dynamic participation of vascular wall damage would implicate congophilic angiopathy as a phenomenon of promotion of multiple pathways of progression in the Alzheimer disease process. Basic aspects of neurodegeneration in disorders such as Parkinson's disease, amyotrophic lateral sclerosis and spongiform encephalopathy would be intrinsic to a process of impaired vasculature and blood supply that are directly related to progressively rapid dementia. Indeed, components of the neurodegenerative process would be paradoxically both primary and secondary contributory factors in progression of the clinical demented state. Regional cerebral hypoperfusion appears one of the

earliest changes in both sporadic and familial forms of Alzheimer's disease[8].

Such a process of primary and several potential secondary factors of progression might be best understood in terms of associative effect rather than simply or solely as evolving cause-effect phenomena in inducing pathologic lesions.

Alzheimer's disease would develop as a manifested attribute of a primary neurodegeneration but would evolve largely in terms of a series of secondary contributory factors that dysregulate control in a variable but sporadic manner. Neuronal and volume loss in hippocampal CA1 region predict duration and severity of the Alzheimer disease process[10].

A FAILED REACTIVE RESPONSE OF INJURED NEURONS

A fundamental biology of inflammation appears intrinsic to neurodegenerative progression in terms of such molecules as COX-2 and CGRP expression[11]. Inflammation may implicate an active participation of inflammatory cytokines and of trophic factors in a manner that integrally damages viability of neurons.

An interactive series of reactions would implicate trophic factor lack with modulators of regional or local blood flow in the development of neuronal cell damage as death phenomena as seen also in viral encephalitis.

Neurodegeneration would implicate an integral reflection of modes of injury to neurons that involve other mechanisms of cell damage, including in particular induced injury due to a lack of responsive reactivity of neurons to neuronal lesions and brain resistance to insulin and insulin-like growth factor I[12].

Neurodegeneration of Alzheimer type might reflect an inability of injured neurons to responsively react to such injury due to a set of conditioning factors related particularly to advancing patient age.

BEYOND A SELECTIVE INDIVIDUAL SYSTEM OF NEURONAL VULNERABILITY

A positive feedback mechanism in the propagation of neurotransmitter effect would perhaps constitute a persistence of influence that implicates neuronal viability in terms also of the neuronal network as a whole[13]. In terms of whole subpopulations of neurons that are not simply individual neurons interconnected together but an integral unity of activity, the actual dynamics of maintained activity would be an expression of neurotransmitter upregulation or downregulation in the face of potential neuronal stimulation.

Given the scope of the trophic effects in terms of neuronal generation and degeneration[14], it might in a sense be important to consider the neuronal networks as integral units of persistent development of neurobiologic tissue. This would contrast with the concept of a developmentally postmitotic nature of the neuronal cell type.

TRANSFORMATION OF THE BIOLOGY OF APOPTOSIS

Apoptosis as a biologic process of evolutionary significance would implicate developmental processes primarily in terms of formation of tissue and organs rather than in purely cellular terms of reference.

Apoptosis is a directly induced mechanism of programmed cell death that essentially would be pathologically derived as an endresult of neurodegeneration.

Neurodegeneration would progress as effects of a transformation of apoptotic mechanisms that strictly account for essential aspects of the disease. A central concept of neurodegenerative progression relates to the integral process of transformation as central to neuronal cell death as apoptosis. Cascades of apoptosis as preprogrammed cell death events would imply a pathologic transformation in terms of both neurodegeneration and as patterned variation.

Alzheimer's disease would implicate not only degeneration of neurons but also morphologic lesions implicit to progression of the cell death pathway. Alzheimer's disease would constitute an expression of the pathology of neurons, glia, vessels and other elements that participate in a basic sequential and concurrent series of events centered on neuronal cell death. A degree of variability in derived cell death pathways would implicate a central mechanism of cell death as pathologically transformed apoptotic series of mechanisms.

Pathologic conversion of apoptotic mechanisms would be a chief determinant in the neurodegeneration of Alzheimer's disease that causes neuronal cell death within the context of dystrophic neurites, synaptic loss, neurofibrillary tangles and of congophilic angiopathy.

It is particularly in terms also of beta amyloid cores that the essential endresult of a burnt out neuritic plaque evolves as endstage Alzheimer's disease.

THE EXTRACELLULAR DIMENSIONS OF THE NEURITIC PLAQUE

Increased density of metallothionein I/II immunopositivity in the Alzheimer cortex would implicate

stimulation of glial cells in the pathogenesis of neurodegeneration[15]. Glial cell proliferation occurs concurrent with increased glial fibrillary acidic protein in terms of an index of neuronal pathology. Heavy metal deposition and binding would be an aspect of the glial cells that actively participate in a process of progressive deterioration in neuronal viability.

Deposition phenomena in the neuropil are implicated in Alzheimer's disease. Fibrillar amyloid deposition leads to synaptic abnormalities and neurite disruption[16]. The essential extracellular dimensions of the neuritic plaques involve the primary microenvironment conditioning leading to progression of a pathologic process that culminates in neurodegeneration.

In terms of an extracellular or microenvironmental influence on cerebral cortical neurons in Alzheimer's disease, the concurrent astrocytic proliferation might constitute an integration of reactive and etiologic elements in neurodegeneration.

Neurons would relate to elements in the neuropil leading to the creation of beta-amyloid cores and other deposits in the extracellular environment of the neuritic plaque.

ABERRANT PROCESS OF NEURITIC DYSTROPHY

A trophic factor would induce neuritic dystrophy in terms linked directly to an evolutionary deposition of beta-amyloid that progresses concurrently with the evolving neuritic dystrophy. Synaptic dysfunction might involve pathogenesis in determining progression of the demented state. Associations of neuritic dystrophy would reflect common overlap mechanisms in synaptic dysfunction.

Concurrent multiple pathways of aberrant development in terms particularly of neuritic dystrophy and of variable synaptic dysfunction would implicate directly astrocytic and microglial factors. Both trophic and atrophic features would be involved in the phenomenon of dystrophic sprouting of neurites in senile plaque formation and also in the neurofibrillary inclusions characterizing the neurodegeneration.

A process of accumulation might transform Alzheimer disease pathogenesis to a dysfunctional state attributable to evolving brain atrophy. Such a dystrophic sprouting of neurites might contribute to synaptic dysfunction in terms of a beta amyloidosis that arises and develops as abnormal trophic influence.

A series of pathways would arise as a result of aberrant trophic influence directly linked to evolving synaptic dysfunction.

Neurites and synapses would be disorganized in terms of aberrant attempts at potential recovery of neurons. Pathologic features central to the Alzheimer disease process are indeed aspects of a process of impaired attempts at preservation of neuronal networks of viability.

ABERRANT TROPHIC EFFECT

Essential plaque genesis would interact with additional progression of gliosis and neuronal cell death in the distribution of pathologic lesions in Alzheimer disease[17]. The neurofibrillary tangles would complement progression in terms limited to neurodegeneration of a slowing evolving type. Beta amyloid deposition would involve neurons and propagate as aberrantly trophic effect. Dystrophic sprouting of neurites would develop as a stage in evolution of the senile/neuritic plaque. The progressive accumulation of a core of beta-amyloid as a focus of increasingly aggregating fibrillogenesis would be analogous to the aggregation of Tau neurofilaments as neurofibrillary tangles within neurons.

The corticolimbic dissemination of lesions is not only distributive but also essentially spreading. This would constitute an expanding process of involvement based on secondarily amplifying and self-propagating influences.

The neurodegeneraton of Alzheimer type is an aberrant trophic effect within the context of both dystrophic neuritogenesis and of neurofibrillary tangle formation on the one hand and of atrophic loss of synapses and dendritic spines and of eventual neuronal cell loss on the other.

ABERRANT NEURITOGENESIS AS A PRIMARY TARGET IN SENILE PLAQUES

Gliosis would operate concurrently with neurofibrillary tangle formation and progression and involve microglial activation and neuritogenesis as inherent aspects of a process of amyloidogenesis[18]. Microglial activation would link gliosis and neurofibrillary tangle formation to a subsequent predisposition to degradation of both glial and neurofibrillary fibers.

The burnt-out plaque would eventually develop as naked cores of beta-amyloid. A true process of degradation of glial fibers and of neurofilaments would evolve as a whole series of events linked to gliosis and to neurofibrillary tangle formation. A series of steps of progression to a burnout out stage of the neuritic plaque would be especially characterized as a loss of the aberrant neurites in such plaques.

MICROGLIAL ACTIVATION AND DEGRADATION OF NEUROFIBRILLARY TANGLES

Microglial accumulation and their phenotypic activation would constitute a phagocytic response in terms of added activity of progression beyond an initial stage of neurofibrillary tangle formation[19]. The association of microglial activation with neurofibrillary tangles might be particularly significant due to a strict sequential series of events that involve degradation of neurofibrillary tangles primarily formed intraneuronally.

Essential events might link a progressive degradation of neurofibrillary tangles with a subsequent evolution in the development of senile plaques specifically related to the dystrophic neurites.

Neurofibrillary tangles would prove a process of progression in terms that constitute a primary form of neurofilament increase and neurofilament autophosphorylation. These would constitute an activation process of intermediate filament formation that is intrinsically linked to possible subsequent degradation. Such degradation of neurofibrillary tangles might be associated with a series of activated microglial responses that additionally implicate neurites that regenerate in a dystrophic manner. Microglial activation would constitute part of the whole microenvironment that induces dystrophy of neurites as part of senile plaque genesis and evolution.

DYSTROPHIC DYSFUNCTION AND TROPHIC LOSS OF ACTION

Dynamics of pathogenesis would involve neuronal loss as a full scale of grades of involvement in a dementing disorder that interacts with structural and dysfunctional attributes of neuronal injury[20].

Neuronal involvement is particularly significant in terms of connectivity[21]. Dementia of Alzheimer type is specifically characterized by tissue cellular damage.

Factors of induced neurodegeneration of whole subpopulations of neurons would contribute materially to the advanced and progressive cortical and white matter atrophy in Alzheimer's disease.

Trophic factor lack would involve loss of action and dysfunctionality of trophic effect in terms of an ischemic-like or para-ischemic phenomenon as induced by impaired blood supply at a microcirculatory level.

A whole system of dystrophic effects would result not only in aberrant neuritogenesis but in an state of neural tissue atrophy inherently progressing as lack of trophic factor effect and due to a dysfunctional activity as senile brain atrophy of Alzheimer type.

CONSTITUTIONAL LOSS OF DEVELOPMENTAL PROGRESSION OF CNS VIABILITY MECHANISMS

Maintenance mechanisms of neuronal viability would actively operate homeostatically to support neuronal subpopulations in health[22]. An active process of developmental progression might perhaps include modes of active process generation of extensive neuronal networks in the central nervous system. Neuronal plasticity would appear particularly implicated in such a central process of maintained neuronal viability.

In spite of the paradoxical inability of neurons to regenerate, it might be valid to consider active developmental phenomena as central to neuronal viability in programming the induction of genetically driven events and in response to direct protein synthesis patterns.

Apoptosis might also be a developmentally progressive phenomenon in neurodegeneration that affects replacement of injured neurons. Only indurect relationship exists between DNA fragmentation and either Amyloid beta deposition or neurofibrillary tangles.

Nerve growth factors would be fully consonant with a central pathway of developmental progression even in the evolving Alzheimer process that affects neurons in a highly selective fashion.

Ischemia or vascular wall impermeability would be pathogenetic factors that interact with systems of dystrophic effect on neurites and synaptic loss.

DYSTROPHIC NEURITOGENESIS AND INDUCED DYSFUNCTION

Aberrant neurotransmission might be an essential facet of overall progression of the demented state and of the neurodegeneration of Alzheimer type[24].

Concerted effect is sustained in Alzheimer's disease in terms of aberrant dystrophic effect that evolves as neuritogenesis and especially as a whole series of subsequent steps in neuronal processing. Neuronal dysfunctionality appears a particularly predisposing factor in the development of tissue brain atrophy. Abnormal neuroglial interaction may lead to reduced growth inhibitory factor in reactive astrocytes and correlates with neuronal cell loss[25].

CONCLUSION

Plasticity of neuronal circuits appears a primary target of pathologic progression in neurodegeneration that reflects onset and evolving definition of the demented state. It might be significant to equate an

atrophic brain of Alzheimer type with a tissue injury that contrasts in various ways with a central concept of individual cell loss.

One might view the overall phenomenon of dementia in Alzheimer's as a full spectrum of continued progression that not only transforms apoptosis dimensions but implicates a further recharacterization of events of evolving injury to multiple tissue components. One might indeed redefine the dementia of Alzheimer type more in terms of an increasing predisposition to further injury as specifically characterized tissue loss.

It is in terms of such atrophic tissue change that one might consider the transformation of pathologic features in Alzheimer's as further development in the overall dynamics of involvement of vessels and glial cells. Neuronal pathobiology would evolve as selective susceptibility traits in the added context of involved dimensions of a process that either injures or else transforms attributes of neuronal circuits.

One might view the development of various indices of change as impaired plasticity of neuronal circuits. In view of the dynamics of such change, one might define the attributes of atrophic brains as a further evolving feature not only of ischemia but also as a realized pathway of developmental tissue loss. The selective neuronal cell loss of progressive severity might implicate a state of susceptibility that predetermines further tissue atrophy.

Apoptosis appears to affect mainly reactive microglia and oligodendroglia[26]. Apoptotic astrocytes are a hallmark of white matter degeneration in Alzheimer's disease[22].

It is significant that attributes of progression are determining features of a process that inherently implicates injury not only at a cellular level but as a further specified determinant in tissue atrophic change.

One might indeed include dynamics of involvement of either neuronal cell loss or of brain atrophy within contexts of progressive loss of plasticity of such components as homeostatically determined fluxes of ongoing progression.

It is only in such terms that Alzheimer's disease would develop further in the characterized overall scheme of ongoing evolving injury to neuronal circuits as contrasted with individual neuronal cell loss.

It is with regard to the development of a transforming attribute in pathogenic progression that Alzheimer's disease might indeed prove an attribute of increasing age of the individual. The specific distinction of Alzheimer brain atrophy from successful brain aging might allow for the overall progression of an injury that is closely correlated with tissue depletion of various components such as vessels and glial cells.

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