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Selective Neuronal Susceptibility as Pathologic Progressiveness in Alzheimer's Disease

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Abstract: Alzheimer's disease might be considered simply a series of pathways of progression in terms of a generic form of pathobiology that is specific to the genomic constitution of the individual patient suffering from the organic dementia. Even in terms of such a paradoxically dual system of influence, however, the central attributes of brain atrophy as a neurodegenerative state might constitute genomic participation beyond a simple concept of selective neuronal susceptibility. Indeed, one might speak of a generic series of steps that determines pathobiologic progression in neurons once injured, and that subsequent evolution to neurodegeneration and neuronal cell death is simply a consequence of such pathobiologic progression versus non-progression. However, in real terms, also, one would perhaps realize a system that is generic in progression but characterized strictly by a genomic constitution that would itself be developmentally a chief determinant in a neurodegeneration as focal lesions of global distribution. Neuronal degeneration and neuronal cell death pathways would perhaps constitute an organic dementia of Alzheimer type largely as a genomic characterization of pathobiologic pathways of progression of neurons injured in potentially multiple different ways ranging from neuroinflammation to associated oxidative injury and vascular ischemia to forms of lipid peroxidation and catabolism.

Key words: Alzheimer, neuronal, susceptibility, pathologic

INTRODUCATION

NEURODEGENERATIVE PROCESSES AS ARISING DIRECTLY FROM AND AS DIRECTLY REFLECTING THE CHARACTERISTICS OF THE GENOME OF THE INDIVIDUAL PATIENT AFFECTED

One fundamental problem with neurodegenerative disorders is the strict delineation of one distinct pathologic entity from another. What constitutes such a variant entity? What criteria essentially distinguish one process of neurodegenerative progression from another. Alzheimer's disease is itself genetically a heterogeneous disorder[1].

Is it perhaps the patient's genetic code itself that ultimately would determine the intrinsic biology of the neurodegenerative process that afflicts the particular individual, a phenomenon apparently less dependent on hereditary factors with increasing patient age at onset of the disease[2]. Is it not relevant perhaps to speak of a neurodegenerative process rather than of a degenerative entity? After all, neurodegeneration, as a pathologic definition would appear essentially meaningless except in terms of a neuronal process that undergoes evolutionary change.

It is perhaps the actual process of a neurodegeneration that would render it distinctive when contrasted to cellular biologic processes of homeostatic control versus pathobiologic progression. In this sense, for example, the Tumor Necrosis Factor (TNF) death receptor pathway and caspases would appear activated in early stages of neuronal degeneration in Alzheimer's disease[3] . Also, Tumor Necrosis Factor RSF6 (member 6 gene) of the TNF receptor superfamily on chromosome 10q would appear to constitute a moderate promoter marker in Alzheimer disease etiology[4].

It might seem that the essential character of evolution of a degenerative process is one that helps identify individuality of distinct neurodegenerative progression in terms for example of susceptibility genes[5] . For example, the expression of different cell cycle proteins in terminally differentiated neurons apparently precedes cell death or contributes to pathogenetic progression in Alzheimer's disease[6].

It is this peculiar property of neurodegeneration not as an essential phenomenon in its own right, but as a form and mode of adoption by the patient's neuron and nervous system as an integral organ that would largely characterize the neurological disease in terms of essential progression.

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Such a concept of centrality of the evolving character of the neurodegenerative process would arise directly from the genomic attributes[7] of neurons, in a way that specifically determines features of the neurodegenerative process in the individual patient as a system of progression that evolves. In this sense, for example, the common receptor for neurotrophins, p75, might be hijacked by various proteins including prion particles, beta-amyloid and possibly tetanus toxoid besides rabies viruses[8].

In a sense, the mode of neurodegenerative progression as either a diffuse or circumscribed form of extension in the cerebrum, the reactive phenomena that might be associated with such extension in the form of free radical-induced damage[9], age of onset pathobiologically and clinically as separately distinct events, its specific mode involvement inducing modality dysfunction, the relationships to various gene mutations such as on chromosome 17, 3, 21, its association with concomitant vascular/oxidative[10,11] manifestations, APOE 4 allele type association, all would tend to indicate the intimate association with the essential genomically inherited attributes of the individual concerned.

Also, for example, platelet amyloid precursor protein analyses might prove valuable as a correlate of putative disease-modifying effects of long term treatment such as with anticholinestase agents[12].

Indeed, identifying genomic features might in real terms constitute the main criterion of unique determination in neurodegenerative progression both in terms of characterization and also in terms of subsequent evolution.

Neurodegenerative processes as evolving processes with dynamic imbalances would appear to induce neuronal loss along one of a potentially highly assorted number of pathways—such variety of possible evolutionary characterization of the neurodegenerative processes of progression beyond any strict categorization might simply constitute real systems of individuality largely constituted by the genomic attributes of neurons both as individual cells and also as constituent neuronal networks.

It is indeed the particularly wide variety and range of gene expression that resides within the central nervous system that would render neurodegeneration a strict system complex of evolving change not simply as adaptative response but particularly as a system of induced transformation that both arises from such adaptative response and also as subsequent effective resolution either as sublethal neuronal injury or as neuronal cell death.

ALZHEIMER'S DISEASE AS BEYOND THE SIMPLE CAUSE-EFFECT RELATIONSHIP IN CONTRAST TO MOST KNOWN OTHER DISEASES IN MAN

A remarkably distinctive feature of the clinical impact of involvement of Alzheimer's disease is in terms of its range of diverse cerebral dysfunctions in that individual patient affected. In a particular sense, the essential evolution of effects of Alzheimer's disease would be analogous to an inexorable defunctionality at successive levels of higher cerebral performance ranging from remote memory loss, intellectual deterioration, speech, visual memory, depression, aggressiveness, motor abnormalities presumably as a reflection of variable forms of escape from mechanistic control involving dysfunctionality of a distinctively depletive nature.

In this sense, it would appear that Alzheimer's disease might truly represent a course of clinical deterioration that reflects a basic pathologic process not simply neurodegenerative but as of a fairly stereotyped pattern of dysfunctionality with loss of integrative capacity, even for example with regard to endothelial function[13]. Indeed with Alzheimer's disease the basic features of progressive disintegrative dysfunctionality of higher cognitive abilities might constitute in effect a disorder of hierarchical disorganization affecting personality, memory, beliefs, aims, driving forces, thinking patterns, mood characteristics, speech eccentricities; indeed, characterization as a system of hierarchical control and integrity as higher cerebral functionality would progressively not only become depletive in type but also dysfunctional in such depletive characterization[14].

In a sense, perhaps, progressive deterioration in a patient with Alzheimer's disease might in a converse sense constitute acquisition of dysfunctional progression in higher cerebral neuronal circuitries that in various ways would be characterized by genomic attributes determining developmental neuronal susceptibility to a variety of potential injurious agents, that would vary according to the individual patient.

Hence, it might in a truly significant manner perhaps prove true that Alzheimer's disease is a system of developmentally depletive nature influencing higher cortical functionality that dysfunctionally characterizes such depletive effect, beyond even simple aspects of pathologic evolution. It might be particularly significant, in fact, that the Alzheimer process is one that gains momentum with increasing age of the individual, an essential aspect of pathobiology of the disease beyond simple cause-effect relationships as would be expected from a simple depletive model for cognitive decline in

organic dementia. Indeed, a state of chronic inflammation limited to lesioned areas can be identified in Alzheimer brains implicating microglia, proteins of the classic complement cascade, pentraxins, cytokines and chemokines[15] .

ONE UNIVERSAL AND ESSENTIAL STEREOTYPED FORM OF NEURODEGENERATION FURTHER CHARACTERIZED IN THE INDIVIDUAL PATIENT BY INNATE PROPERTIES OF GENOMIC AND DYSFUNCTIONAL PROGRESSION

What is the role or position of genetic linkages[16], for example, of mutations/polymorphisms of the tau gene on chromosome 17 as seen in association with frontotemporal dementia, in the added general context of sporadic occurrence of dementia cases?

One possibility, of course, is that a genetic association would represent a form of susceptibility to the development of neurodegeneration, a concept that could potentially be significant in terms of implied specific pathways of progression leading in various ways to an increased tendency for such evolving neurodegeneration[17].

How might neurodegeneration, particularly decreased viability of neurons within distinct neuronal networks, be specifically predisposed to?

Certainly, the distinctive occurrence of such significant overlap of clinical and pathologic features between many different cases of dementia, might constitute in fact a specific attribute of neurodegeneration as a generic disorder of variable expression ranging from a lobar type of frontotemporal dementias, to Alzheimer's disease, Diffuse Lewy Body Disease with features also of Alzheimer type, dementia associated with features of amyotrophic lateral sclerosis, or to the occurrence of Pick type pathology within a described concept of "Pick disease Complex". In addition, an important degree of variability not only in forms of presentation clinically and pathologically of certain classic cases of dementia, would perhaps itself help redefine neurodegenerative progression as simply generic systems of progression and of genomic characterization.

Indeed, parietal involvement in patients with otherwise Classic Pick Disease, or development of dementia in patients with otherwise classic progressive supranuclear palsy, or even the highly significant degrees of variability within the integral group of Alzheimer's disease itself in terms of both clinical (for example, age of onset, rate of progression of the dementia) and also pathologic characterization for example in terms of the presence of Lewy Bodies in the cerebral cortex) would in themselves constitute effective aspects of redefinition of a process of evolving progression as neurons either degenerate or die in patterned distribution. Even the strict occurrence of dementias as an apparently primary subcortical neurodegeneration would appear to render strictly valid distinction between cortical versus subcortical pathology in various cases of neurodegeneration.

Certainly, the emergence clinically of a complex of dementia is itself presumably one intrinsically heterogeneous in nature not only clinically but especially in terms of pathologic, pathobiologic and biochemical criteria.

Of course, intricate degrees of integrative structure and function of the central nervous system would specifically characterize neurodegeneration specific conditions of paradoxical generic nature. Even the term "neurodegeneration" would itself essentially constitute systems of effectively nature generic type with a full assorted range of potential progression beyond simple etiologic and pathogenic cause-effect relationships.

In spite of such considerations, however, characteristic properties exhibited by neurodegenerative disease and of dementia disorders in particular would perhaps determine establishment of pathobiologic progression as evolving neuronal damage beyond specific process activity. Paradoxically, it might be true that the term "neurodegeneration" would itself redefine genomic attributes of neurons as a basic biology of progression induced by the patient's integral constitutional state .

Such a concept, for example, would modify conceptually the neurodegenerative process in terms of a characterization of parameters of progression anatomically and regionally in the cerebrum[18] , beyond simple cortical versus subcortical regionality, of spinal cord versus cerebrum or even in terms of actual nature of relationships of neurons with glia in organic dementia or in motor system disease. Indeed, inclusion bodies in glial cells (oligodendrocytes) and astrocytic manifestations of involvement in dementia cases as either tau inclusions, or even the gliosis in Pick's disease or the microglially associated neuroinflammation[19] would perhaps help strictly redefine neurodegeneration as a manifestation specifically reflecting progression pathways in neurons. Beyond a simple categorizing approach to neurodegeneration or dementia, one might actually be confronted by multiple potential pathobiologic pathways of initiation, evolution and progression resulting eventually in neuronal death and cerebral or regional atrophy that are specifically characterized as genomic attributes towards progression.

Perhaps, characterization of cases of neurodegeneration and of dementia would ultimately depend on specific susceptibility traits in that individual

patient as determined by genetic constitution that severely modifies or otherwise determines definitive dynamics of progression of neuronal injury and neuronal death pathways in terms of a neurodegenerative disease. Indeed, a strict redefinition of the nature of neurodegeneration might simply involve an integrally effective resolution of genomically determined susceptibility in the face of evolving progression of such genomically determined susceptibility to neuronal injury. It might very well be true that neuronal cell death on a zonal or global scale as seen in neurodegeneration would constitute stereotyped phenomena elicited by the patient's genome as a pathobiology of generic progression pathways. Indeed, in a strict sense, a pathobiology of progression pathways might constitute a single real determinant in terms of both expression and of effective consequence of neurodegeneration in any one individual.

AGAINST A "SPECIFIC DISEASE ENTITY" DIAGNOSTIC APPROACH TO PRIMARY NEURODEGENERATION OF THE BRAIN

It is certainly fundamental to recognize the importance of the presence or absence of dementia as a main reference point in defining the strict pathology of many forms of neurodegeneration from corticobasal ganglionic degeneration, to progressive supranuclear palsy, frontotemporal dementia, Pick's disease, or "tangle-only" disease. This is true even though clinical criteria have generally been recognized as rather less specific definitions of morphologic and immunohistochemical findings.

It is this centrality of as an existing or nonexisting clinical demented state that would give distinctive character to primary sites of neurodegeneration. Such a concept would indicate that the cortical neuronal population with its associated neuronal circuit patterns of interdependence would constitute fundamentally integral organs with distinctive pathologic profile especially as redefined pathways of pathobiologic progression as represented by beta-amyloid deposition [20].

This is true in spite of the fact that one might realize that morphologic degeneration as simply a series of patterned disorders of distribution of lesions ranging from neurofibrillary tangles, neuronal loss gliosis, neuropil threads, to swollen neurons.

Certainly, the tau filaments[21] with their characteristic aggregation[22] and other ultrastructural features such as filaments or tubules as doublet or triplet arrangement of variable size dimension, together with their immunoelectrophoretic mobility and specific immunohistochemical staining would add a further dimension of significant pathways of pathobiologic progression in neurons when injured[23] .

Attempts to combine various distinctive criteria into new integral schemes of susceptibility as specific disease entities in an individual patient might simply implicate a direct participation by neurons that respond variably to injury that is generic in type. For example, genetic association between APOE 4 and Alzheimer's disease might depend on greater nitric acid production by microglia in APOE 4 carriers, with subsequent higher risk for oxidative/nitrosative stress injury to neurons[24] .

Is it significant to distinguish pathologically between corticobasal ganglionic degeneration from progressive supranuclear palsy? Even the classic individual lesions and patterns of distribution of one or other neurodegenerative disorder causing dementia might simply constitute attributes specifically of neurodegenerative progression rather than of neurodegeneration per se. It is in this sense that neuronal constitutional participation would in a final analysis determine neurodegenerative attributes of a patient's involvement simply or largely in terms of patterns of pathobiologic progression pathways in such neurons. It is for example the confirmatory morphologic features generally characteristic of progressive supranuclear palsy with added cortical involvement as seen in a few cases that would perhaps help redefine neurodegeneration as a specific pathway of paradoxically generic dimensions. It might be a fundamental pathologic attribute that a specific disease entity would progress only as a neurodegeneration that is specifically categorized in that individual patient affected by the demented state. It would perhaps be true that primary neurodegeneration affecting the brain involves a "specific disease entity" only as a specificity of progression arising from determinants of genomic susceptibility type as for example with the APOE epsilon 4 allele[25].

Such a concept might itself also overlap pathobiologically with a concept of selective vulnerability of neurons as an expression of generic progression pathways of influence in the highly specific context of the individual patient with organic dementia. In this sense, for example, the gene CYP46 which encodes cholesterol 24-hydroxylase would influence brain and Cerebrospinal Fluid Beta-amyloid loads and phosphorylated tau and the genetic risk of late-onset sporadic Alzheimer disease[26].

ALZHEIMER'S DISEASE AS A PROGRESSIVELY DYSFUNCTIONAL STATE INITIATED ON A PURELY ORGANIC BASIS

A particularly interesting point is the related occurrence of amyloid angiopathy and of Beta-amyloid

deposits within neuritic plaques in Alzheimer's disease as a full range of variant cognitive dysfunction. Alzheimer's disease might essentially be considered a morphologic spectrum of variability, terms of expression clinically and pathologically that is essentially incorporated within an overall scheme of relentlessly progressive cognitive dysfunction.

And here perhaps is to be identified the central significance of amyloid deposition in the brain[27] that somehow associates with predominant and irreversible cognitive dysfunction in a context of strictly organic dementia. It is such apparently strict relation with regard to specific types of morphologic change of variable magnitude but as strict patterns of distribution of focal lesion involvement that would render Alzheimer's disease an expression of generic constitutional upset involving progression versus non-progression of processes such as injury due to neuroinflammation[28] . Such association of morphologic lesions with concurrent amyloid deposition would help indicate the presence of pathways of dynamic evolution not simply as Beta-amyloid deposition in the neuritic plaque but particularly as patterns of association between cortical neuronal pathways and angiopathy defined pathobiologically as integrally progressive pathways of potentially interactive nature[29,30]. Alzheimer's disease as an expression central to evolving pathways of developmental nature involving pathobiologic progression would essentially constitute a series of evolutionary consequences both arising and developing as an essential organic dementia.

Alzheimer's disease, in an important sense, might constitute an expression of how generic pathobiologic processes are themselves highly specific pathologic lesions in their own right because of dynamic evolutionary consequences of such neuronal involvement.

That in fact, such a common condition as Alzheimer's disease would constitute generically a disease of consequential progression in terms of pathologic involvement of neuritic processes and their connections might simply implicate synaptic integrity as a site of persistent activity determining progressiveness of the organic dementia process.

A focality of neuronal involvement in terms specifically of a global brain atrophy would in real measure constitute a basic pathobiologic expression of neuronal susceptibility in that individual patient that subsequently is consequential largely as progression pathways of neuronal susceptibility.

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