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Aberrant Cytoskeletal Sprouting of Axons Induces Denervation Atrophy in Amyotrophiclateral Sclerosis

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Abstract: Toxic gain of function affecting motoneurons and neuromuscular junctions would operate as a pathogenetic system of injury to neurofilaments and cytoskeleton of axons and neuronal cell bodies. Oxidative stress appears directly implicated in the development of a disease that evolves largely as loss of neurons in the anterior spinal horns of gray matter and as extensive loss of axons in the corticospinal tracts. The evolution of denervation atrophy of multiple groups of myofibers appears an integral component of this toxic gain of function mediated by oxidative stress and operating at least in part as also a primary site of disease involvement. It would appear that amyotrophic lateral sclerosis is one aspect of a whole series of possible outcomes of a diseased neuronal phenotype that evolves in terms of cytoskeletal and neurofilament pathobiology bridging aberrant axonal sprouting, synaptic loss and neuronal cell loss.

Key words: Aberrant cytoskeletal, induces denervation, amyotrophiclateral sclerosis

INTRODUCTION

TOXIC GAIN OF FUNCTION IN CYTOSKELETAL SPROUTING OF AXONS IN ALS

A neuroprotective regimen as a modulated prevention of progression of amyotrophic lateral sclerosis (ALS) would evolve in terms of prevention of a neuronal injury that progresses in retrograde fashion. Pathology of the neuromuscular junction and the combined degeneration of both upper and lower motor neurons might implicate injury leading to abnormal synaptic vesicle release and neuronal cytoskeletal damage. A current hypothesis implicates loss of a muscle-derived neurotrophic factor acting together with normal age-related deterioration and loss of motoneurons[1].

Axonal neurofilaments are a potential target for therapeutic intervention in terms of regenerative sprouting of terminal axons with cytoskeletal disarray and neuromuscular junction loss. A regulated T cell response to a progressive cytoskeletal injury of sprouting axonal terminals might lead to a neuronal pathobiology with cytoskeletal pathology and impaired synaptic vesicle release reflecting neurofilament loss or slowing. In general terms, environmental factors such as viral infection or inflammation together with innate immunity may cooperate to influence the course of ALS[2].

Binding of mutant copper-zinc cytochrome dismutase with heat shock proteins would appear to involve a series of reactive changes that accentuate injury to transport or trafficking systems along axons together with progressive cytoskeletal injury.

The involvement per se of both upper and lower motor neurons in amyotrophic lateral sclerosis would reflect a series of aberrantly transformed terminal sprouting and synaptic loss as endpathways of neuronal atrophy and cell death, involving possibly perturbations in endosomal dynamics[3].

A toxic "gain-of-function" linked to copper ion insufficiency at the copper site of the superoxide dismutase molecule appears a possible initial point that may implicate loss of viability of the cells as aberrant terminal axonal sprouting resulting in cytoskeletal pathology of the neuron and in neuromuscular junction loss. Also, in common with many other neurodegenerative diseases, there is aberrant nitric oxide synthase III (NOS III) expression and NOS III-associated neuritic sprouting in the CNS in ALS (2). A role for zinc in neuronal cell death in the CNS also needs to be investigated[4].

Toxicity to neurons might be implicated as incrementally increased neuronal injury with possible attempts at recovery of individual axons.

Axonal sprouting constitutes a coordinated series of pathways targeting variably established integrity of axons and synapses. Projected mechanistic processes would appear centrally implicated in disruption of neurofilament continuity as intracellular filament disarray. There is accelerated loss of motor units in ALS, with abnormal adaptive sprouting followed by maladaptive sprouting and recession of terminals[5].

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Evolving neuronal injury affects also upper motor neurons in cerebral cortex and brain stem that are vulnerable to a disease process involving toxic gain of function implicating superoxide dismutase.

One might perhaps interpret toxic gain of function as simply a transformed functionality that disrupts energy provision and uncoupling of energy stores with impulse conduction pathways[6].

LOSS OF ADHESION CONNECTIVITY AS A TOXIC GAIN OF FUNCTION IN ASL

Amyotrophic lateral sclerosis implicates loss of neurons that is specifically related to denervation of multiple skeletal myofiber groups in the body. The loss of neuronal cell bodies and their axons accompanies loss of the neuromuscular junction as a denervation that progresses as group atrophy of individual myofibers. This may possibly reflect defects such as loss of glial glutamate transporter 1 in certain forms of ALS[7].

Such group myofiber atrophy would reflect group dropout of neurons that essentially characterizes amyotrophic lateral sclerosis. A rigid separation of pathogenetic mechanisms into neuropathy, axonopathy and myelinopathy may not be always possible[8].

In terms of such group loss of neurons in the anterior spinal horns of gray matter, amyotrophic lateral sclerosis would evolve largely as a cell injury implicating either non-programmed or programmed cell death pathways. The brainstem and cerebral involvement in this disease appears largely a concurrent series of events based on a similar process of lower motoneuron loss as an integral pathway[9].

Accounting for a neuronal cell death primarily affecting axons rather than neuronal cell body might help account for dynamics of a disease process inducing an initial denervation of groups of skeletal myofibers. Reinnervation of the skeletal muscle by nerve sprouting in ALS may involve previously denuded postsynaptic regions. The preserved postsynaptic regions including acetylcholine receptors, the basement membrane and Schwann cells may play an important role in such a process[10].

Superoxide dismutase would operate as a system of toxic gain of function irrevocably damaging suborganelle systems of transport and sprouting of axons.

Caspase 12 and the endoplasmic reticulum pathway for cell death may constitute targets for treatment in ALS[11].

Impaired blood supply and retrograde atrophy of axonal tracts might operate as integral extensions of primary axonal and primary skeletal myofiber loss that lead to synapse loss at interneuronal and neuromuscular junctions. Collateral axonal sprouting fails only in the latest phase of paralysis[12].

Synapses as endorgans of innervation might imply a long term dependence of various pathways potentially progressing as group neuronal loss. Synaptic detail confirms the presence of abnormal end-plates and axonal sprouting concurrent with the denervation[13].

It is in trying to distinguish an individual cellular involvement in amyotrophic lateral sclerosis that progresses as group atrophy of skeletal myofibers that one would redefine systems of amplified propagation affecting groups of neurons and groups of myofibers.

Variability in group involvement of skeletal myofibers is characteristic of a disease process that primarily depletes synapses. Upper and lower motor neuron atrophy and synaptic involvement would lead especially to denervation of skeletal myofibers, possibly through mediated action of immune serum factors that suppress axonal sprouting[14].

Pathway progression affecting axonal and myofiber units might implicate synaptic loss together with an overall loss of intermediate filament contact and disturbance in axonal transport and cytoskeletal connectivity. Loss of contact pathways with axonal disarray of neurofilaments accompanies denervation of groups of skeletal myofibers.

Studies with transgenic mice suggest that accumulation of some intermediate filament types in ALS lead to neurodegeneration. In fact neurofilament gene mutations may be linked to ALS and Charcot-Marie-Tooth disease[16]. Accumulation of midsized neurofilament subunit may induce motor neuron disease in transgenic mice[17].

Neuronal dropout as loss of axonal contact and loss of synapses constitutes essential progression in amyotrophic lateral sclerosis in terms of a group denervation atrophy of skeletal myofibers.

Such denervation of myofibers would constitute only one facet of an integral disease process that culminates in respiratory failure. Upper and lower motor neuron paralysis constitutes denervation of groups of skeletal myofibers concurrent with primary pathways of axonal loss that evolve beyond neuronal atrophy. CREB in particular exerts neuroprotective functions. CREB binding protein is a new caspase-6 substrate. Fine adjustments of hostone acetyltransferase and CREB binding protein activity is necessary to ensure neuroprotection[18].

Lack of axonal transport with myofiber denervation atrophy would implicate the neuronal cell body as a prime target for progression in amyotrophic lateral sclerosis. ALS appears to constitute a distal axonopathy with dying

back degeneration towards the neuronal cell body[19].

Neuronal cell body atrophy as a loss of contact between intermediate filaments would extend from axons to neuronal perikaryon. An atrophic process bridging groups of skeletal myofibers and pathways of upper and lower motoneurons would perhaps redefine a process of amyotrophic lateral sclerosis that impairs interactive contact at synapses.

Superoxide dismutase mutants would help reclassify dynamics of synaptic and trans-synaptic progression in amyotrophic lateral sclerosis. Oxidative stress seen in both familial and sporadic ALS may only be one post-translational mechanism affecting specific proteins essential for neuronal stability and health. Protein cross-linking by transglutaminase paralleling may induce dysfunction of proteasomes and may be significant in the evolution of ALS[20].

Toxic gain of function appears a concept arising directly from dynamics of a disease process affecting interactions between neurons and synapses. Cells are not only targets of ALS pathology but also a primary source of involvement as transformations of suborganelles and as biochemical lesions.

Superoxide dismutase mutants affect adversely whole subpopulations of neurons as oxidative stress injury that mediates effects attributable to hypoxic-type injury. Biomolecular oxygen would perhaps be effectively replaced by superoxide radicals that persist in the presence of a toxic gain of function of superoxide dismutase mutations.

SELF-PROGRAMMING OF CELL BODY ATROPHY AS AXONAL DEGENERATION IN ALS

Neuronal cell dropout appears distinct from dynamics of a self-programmed death pathway. Indeed, implications of a cell pathology primarily concerned with long axonal outputs might project as a disease process that relentlessly progresses in an age-specific manner.

In this sense, self-programming in terms of patient age might help account for an embryonic determination in onset of neuronal cell death that is specifically not apoptotic. Indeed, one might perhaps view the pathologic process in amyotrophic lateral sclerosis as largely one of progressive atrophy of projections and of cell bodies that innervate multiple groups of myofibers.

The motoneuron specificity in amyotrophic lateral sclerosis would arise as a partial denervation that progresses as an integral event of skeletal myofiber atrophy. Neuronal dropout is primarily a programmed series of concurrently progressive cell body atrophy with axonal involvement[20].

Stages in a process of evolving neuronal injury that is progressive might implicate a variability of response on the part of the cell that is self-defined. Such self-defined programming of neuronal injury and recoverability might attest to a series of reactivities that arise as toxic gain of function in eventual neuronal dropout in amyotrophic lateral sclerosis.

Long axonal pathways are preserved systems of induced synaptic transmission that evolve both in anterograde and also retrograde fashion in relation to a possible focus of injury. It is perhaps in terms of a reactivity that implicates many pathways that one might redefine amyotrophic lateral sclerosis as potential evolution subsequent to synaptic loss. Various forms of ALS may relate to defects in axonal maintenance. Axonal growth defects in particular appear especially implicated in spinal muscular atrophy. Axonal transport of mRNAs for beta-actin and other proteins may be affected, including also local translation of proteins in the distal axon[21].

Neurofilament subset involvement would appear to reflect axonal participation in ALS that is predominantly self-determining in terms of injury to the cell body. A parallel analogy with apoptotic cell death appears primarily a characterization of events that strictly defines neuronal cell dropout as cell atrophy and as neurofilament involvement.

A DEFICIT IN BIOMOLECULAR OXYGEN SUPPLY AFFECTS MOTONEURONS IN ALS

Altered energy provision to motoneurons appears central to the selective vulnerability in the onset and progression of amyotrophic lateral sclerosis. Indeed, ALS might specifically affect systems of mitochondrial metabolism that are concerned with Na/K ATPase regulation on the one hand and with free oxygen radical formation and scavenging on the other[22].

Cu and Zn binding sites of mutant superoxide dismutase are a source of mitochondrially mediated progression of cell death that operatively evolves as disturbed provision of energy to subcellular organelles. This would evolve in a context of altered expression of vascular endothelial growth factor receptor subtypes in the spinal cord that reflects the complex reactive processes concurrent with neuronal injury[23].

Intermediate filament participation in safeguarding integrity of long axon pathways of motor neurons would perhaps provide a mode of progression in neuronal injury that promotes apoptosis.

Transgenic models of mutant SOD1 but not

homozygous deletion of the SOD1 gene might account for a series of pathways that would modify or otherwise alter disposition and utilization of oxygen and of free oxygen radicals by motor neurons.

In a special sense, the actual utilization of molecular oxygen by neurons would implicate scavenging of free oxygen radicals beyond apoptosis or even neuronal cell injury per se, including especially defects in neurofilament transport in axons[24].

A basic concept of evolving susceptibility to neuronal injury in ALS might perhaps involve oxygen insufficiency that somehow impairs the neuron's ability to recover from stress as induced by various mutant forms of SOD1 that expose the cells to accumulating free oxygen radicals.

It is significant that ALS is age-related in a specifically evolving manner that would transform neuronal handling of stressful stimuli to increasing insufficiency in oxygen supply to the neurons. In this sense, the mounting accumulation of free oxygen radicals would implicate insufficiency of oxygen supply in parallel with neuronal cell death.

A VARIABILITY IN APOPTOTIC SIGNALING INDUCES A RELATIVE SPECIFICITY IN AGE-PROGRESSION IN ASL PATIENTS

A multitude of pro-apoptotic signals possibly operates to alter viability of motoneurons in ALS. In the same manner that multiple components with pro-apoptotic and anti-apoptotic attributes would contribute to the apoptotic cell death of neurons, there also exists a sequence of multiple components that varies with effective induction of the apoptotic signal.

Various signal pathways such as hypoxia and free oxygen radicals would induce variability of progression of a disease process that is primarily age-related.

Age-specificity in the onset and progression of the ALS disease process would allow variability of involvement as a parameter in progression of neuronal cell death in various disease processes including amyotrophic lateral sclerosis.

Only in so far as such variability of response and effect in disease progression relates to a specific age of onset of ALS can one perhaps consider how hypoxia inducing neuronal cell death is a possible cofactor in SOD1 mutant generation of oxidative stress.

A PARALLELISM OF MOTONEURON CELL LOSS AND OF DENERVATION ATROPHY OF MYOFIBERS TRANSCENDS SIMPLE CONCEPTS OF APOPTOSIS IN ASL

Recruitment of a neurodegenerative phenomenon that implicates a relentlessly progressive neuronal cell death pathway appears to characterize a whole variety of cellular transformation events linked intrinsically to how the neurons in fact function as motor impulse pathways in innervating skeletal muscle. In such a context, Insulin Growth Factor 1 is a potent life signal to motoneurons[25].

Neurons die due to the influence of transforming mechanisms in progression of the ALS disease process.

The SOD1 mutants would constitute one mode of influence in predisposing cells to a relative lack of molecular oxygen in a context of a changing milieu affecting free oxygen radical generation. Recruiting generation of free oxygen radicals might in effect prove a predisposing mechanism in the creation of a hypoxic environment. Lack of biomolecular oxygen supply to large neurons would involve corticospinal axons as a primary target..

A brain and spinal cord dichotomy of effects in ALS pathology would evolve simply in terms of a denervation of skeletal myofiber groups that is irreversibly conducive to cell atrophy. The neuronal cell loss would correspond to such a denervation atrophy of skeletal myofibers that is primarily associated with neuronal and synaptic loss due to axonal cytoskeletal injury and neurofilament disarray.

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