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Essential Distributional Conditioning in Motor Neuron Diseases. Is Plasticity Implicated in Systems Biology of Disease?

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Abstract: Dynamics and mechanics of expression of disease biology are symptomatic of an aberrant homeostatic mechanism affecting primarily the corticospinal tract within the scope of developmental biology of motor neuron diseases. It is significant that full development of plasticity mechanics and loss of such plasticity is the cause of loss of trophic maintenance of the skeletal myofiber as component systems of the integral motor unit. The neuromuscular junction as a site of plasticity in its own right would complement the integrative functionality and homeostatic mechanics of involvement of a whole broad range of lesions in motor neuron diseases that contrasts with the universal and relatively simple clinical expression of myofiber atrophy. It would further appear that consequences of motor system biology of disease are symptomatic of genetic consequences in terms beyond simple mechanics of trophic deprivation. A toxic gain of functionality of lesions consists of cardinal features of a progressiveness of involvement as exemplified by mutations in Copper/Zinc superoxide dismutase in some familial forms of amyotrophic lateral sclerosis.

Key words: Motor neuron, systems biology, plasticity, microenvironment, conditioning, dynamics

INTRODUCTION

It would appear that a serial set of events as sequential consequence to particular or specific circumstances integrate as motor neuron diseases as evidenced by determined phenotypic traits characterizing given individual patients affected as prototypes of the disease entity. This includes spinal muscular atrophy due to loss of function of SMN1 involved in splicesomal small nuclear ribonucleoprotein assembly (Rossoll and Bassell, 2009). It is especially significant to view the ranges of expression of motor neuron involvement in a manner that specifically incorporates tract selectivity in disease evolution.

The seemingly expressive mode of participation of neuronal oxidative stress as typified by some cases of familial disease in particular might include the interactive involvement of a serial sequence of pathway consequences in a pre-defined manner. TDP-43 redistribution appears an early event in sporadic Amyotrophic Lateral Sclerosis (ALS) (Giordana *et al*., 2009). Tissue modelling and tract selectivity appear especially implicated in the evolutionary development of neuronal atrophy, neuronal loss and the characterization of skeins and other types of inclusion bodies. The replicative capability of injurious events would implicate a modelled participation of the changes in neuronal viability that is especially progressive and depletive. Survival Motor Neuron (SMN) protein is a potential determinant of ALS severity (Turner *et al*., 2009).

The concept of a centrality of affliction of the anterior horn cells in the spinal cord contrasts with the loss of Betz cells in the cerebral motor cortex as further expansion of the forms of involvement of the neuronal population extends to pathways closely allied to variability of disease expression.

MATERIALS AND METHODS

Disease phenotype: The etiologic considerations that reach defined expression as disease phenotype might clinically categorize disease involvement in terms of lateral sclerosis or as upper motor neuron predilection. The skeletal muscle atrophy originates in terms particularly of a denervation phenomenon as defined pathogenic involvement of preset dimensions including chronic dysregulation of the intracellular Ca (2+) homeostasis (Ragancokova *et al*., 2009).

Dimensional preservation of the range of motor neuron affliction might allow for a redefinition of the biologic involvement of corticospinal tracts in particular. A significant contributing role is the expressive progression of the denervation of skeletal muscle in terms that are strictly and directly pathogenic of further

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involvement by etiologic causation of new lesions. The strict necessity in recognition of the causative participation of a whole array of interacting pathways appears a dominant influence in the recognizable involvement of the corticospinal tract. Administration of human marrow stromal cells through cerebrospinal fluid prolongs survival in experimental amyotrophic lateral sclerosis (Zhang *et al*., 2009).

The overall dimensions of disease involvement appear a prominent range of affliction that is integrally expressed as neuronal cell loss. The question of an individual neuronal cell death phenomenon would insufficiently account for the corticospinal tract involvement beyond simple dynamics of cell loss. One might conclusively recognize disease dynamics in terms of the overall projection of integral fiber tracts in defining the patient involvement by pathology of the motor neurons. In terms specifically arising within contexts of further evolving lesions the motor neuronal pathways are significant as specifically and functionally definable tracts of a neuronal body origin. TDP-43 defines a novel class of neurodegenerative disorders as TDP-43 proteinopathies (Liscic, 2009).

The semblance of neuronal body loss is a significant element in defining a lesion that incorporates neurofilament pathology. The especially prominent progression of the lesions is further amplified as significant participant in disease phenotype determination.

Neurodegeneration of amyotrophic lateral sclerosis is the unfolding expression of a series of injuries of determined sequential identity and as further furnished in defining evolutionary dynamics (Xu *et al*., 2009). The occasional finding of neuronophagia might significantly implicate an initial axonal dying back phenomenon but is especially significant also in terms of the roles of participation of the individual motor neuron body in defining the dynamics of progression and selectivity of corticospinal tract pathology.

Evidence of chromatolysis as a sign of neuronal cell death or injury is the central expressive form of a cellular lesion that implicates neurofilament loss.

The trafficking injurious agent as postulated lesion in amyotrophic lateral sclerosis might be invariably a disease expression of corticospinal tract involvement. Predominant mitochondrial alterations in proximal axons may lead to disrupted axonal transport (Sasaki *et al*., 2009). The participation of the individual motor neuron in terms arising paradoxically from pathology primary in the corticospinal tract would appear the consequential expression of the disease as this progresses within a context of tract projection rather than as individual neuronal cell death. The neuron-astrocyte synaptic complex is a fundamental operational unit of the nervous system (Yang *et al*., 2009).

Corticospinal tract: The undefined lesion originating as corticospinal tract involvement in the first instance would signify the dimensions and dynamics of pathology of amyotrophic lateral sclerosis. Loss of ALS2/Alsin function in neurons is significant in spinal motor neurons but not cortical neurons (Jacquier *et al*., 2009).

The individuality of the lesions at the level of the neuronal cell would further contrast the significant roles played by cell body and axonal spheres of affliction in disease progression. Mutations that affect pre-mRNA processing are the cause of many genetic diseases, targeting especially cis-acting regulatory sequences in a given transcript (Chari *et al*., 2009).

One might allow for the interactions of an apoptosis of the neuronal cell within contexts of the activation of the individual cell body. The reactivity of the injurious event seems allied to the scope of progression of the main pathologic expressive nature of the disease entity. Differential response to neurotrophins and myelin-associated glycoprotein by corticospinal neurons involves independent corticospinal tract axon and dendritic outgrowth kinetics (Richter and Roskams, 2009).

A conceptual defect in neuronal homeostasis is a prominent feature of the disease as defined pathologic entity in its own right. There is significance in the recognition of various multiple lesions as borne out by individuality of neuronal affliction and as motor tract expression of a primary type. The whole developmental characterization of involvement might allow for the progression of the injury beyond definable identity of the individual cell pathology. In this sense the individual neuron is itself an expression of tract involvement extending in variable extent from the motor cerebral cortex to the neuromuscular junction incorporating denervation atrophy of the skeletal muscle fibers. Nitrated proteins are promising candidate biomarkers for early diagnosis of ALS (Nardo *et al*., 2009).

The dimensional resolution of the lesions in amyotrophic lateral sclerosis would underlie the full characterization of a given strictly defined primary lesion in terms that encompass progressive denervation of multiple skeletal muscle groups. The participation of the integral motor unit contrasts with a primary corticospinal tract pathology in terms that refer essentially to dynamics of interactivity and of further progression of the lesions in the neuronal cell body. Motor neuron cell bodies accumulate mitochondria derived from the distal axons projecting to skeletal muscle (Martin *et al*., 2009). The

variability of involvement of individual neurons is significant as models of expression of a disease phenotype that is primarily unstable as lesion predetermination.

Patterns of resolved expression of corticospinal pathology are the dominant phenotype predetermination of amyotrophic lateral sclerosis. Genetic background exerts a strong modulatory effect on the toxicity of aggregation-prone proteins in conformational diseases (Gidelevitz *et al*., 2009). Overall significance of injury at a cellular level arises as interactivity with glial cell reactivity pattern involvement. The biologic context of evolution of a lesion is predominantly a recharacterization of the participating roles of glial cells at the level of the individual neuronal cell body. The neurofilament involvement is an expression of such glial cell participation and in terms beyond simple definition of mitotic cell activity by an otherwise permanent neuronal phenotype.

RESULTS AND DISCUSSION

Multiple levels of expression: The whole scope of the participating lesions as aggregate phenomena in their own right might account for different multiple levels of expression of the motor unit. A polygenic multifactorial etiology is implicated (Eisen, 2009). The interactions of motor units with a corticospinal tract involvement would signify a resolved characterization of an idiopathic lesion determination within further fields of progression of the disease. The advancing progression of fields of involvement in amyotrophic lateral sclerosis is significant as specific characterization of a full series of patterns of participating influence.

The dimensions of such pattern characterization would allow for the dynamics of progression of the disease as both individual neuronal affliction and also as motor unit pathology as further exemplified by a primary corticospinal tract involvement. Synapse formation at the neuromuscular junction requires an alternatively spliced variant of agrin that is produced only by neurons (Ruggin *et al*., 2009).

Models of further progression in disease severity contrast with an expansion in lesion affliction afield and beyond the dimensional characterization of the morphologic attributes of a given corticospinal tract.

Patterned lesion creation implicates dynamics of involvement that progress further within contexts of alternative participation by corticospinal tract pathology. Both autophagy and mitochondrial content are implicated in regulation of neurite length and function in plasticity and pathological remodelling (Chu *et al*., 2009).

The significance of extended individualization might be a chief determining factor in characterization of the injury to neurons. Glial reactivity and neuronal cell loss are featured lesion progression as determined by specifics of a dynamic turnover of various compounding influence primarily at the level of the corticospinal tract.

Individualization in lesion infliction would indicate a range of variable factors in pathogenesis. Post-translational mechanisms may modify protein levels (Spadoni *et al*., 2009). One would view the combined participation of various etiologic influences in terms of the ongoing characterization of new forms of already established lesions. The hierarchical evolutionary involvement of neurons would indicate a semblance to injury of multiple cellular component organelles. In this sense, the neuropathologic patterns would further characterize the defined phenotype of a lesioned neuron and as tract involvement.

The reliability of involvement of individual neurons as patterned lesion creation would perhaps allow for the definition of injury at multiple levels of resolution of the lesion. Genetic factors contribute to determination of susceptibility to motor neuron degeneration. ALS is more genetically heterogeneous than previously recognized (Chio *et al*., 2009). Indeed, one might postulate a proto-type lesion involvement from which arise a propagated series of injuries as neuronal and glial cell interaction further afield.

Sequential expression: The characterization of a lesion is simply an expression of a sequential process of identifying sites or foci of possible new injury (Rothstein, 2009). The remarkable participation of inclusion body formation might significantly identify the process of neuronal cell atrophy and loss in terms of ongoing creation of new lesions further afield. The realization of influence might signify a resolved definition in terms that allow progression of the neuronal cell loss. A glial reactivity would further compound the lesion involvement as dictated by modelled participation of neuropil or stroma.

It is in terms of over-expression of the injury that there would develop a sequential characterization of individual lesions. Predetermined influence might also allow for the significant redefinition of injury as homeostatic upset of the neuronal microenvironment. Denervation and reinnervation comprise a dynamic process that begins early in the course of amyotrophic lateral sclerosis and lasts until the final individual motor neuron dies (Bek *et al*., 2009).

The complexity of nomenclature of motor neuron diseases revolves around distributional patterns of

clinical and pathologic involvement of the nervous system as strictly related to dynamics of expression of muscle weakness and paralysis. The whole panoramic scope of involvement of the corticospinal tracts in primary lateral sclerosis is itself an expression of the involvement of the skeletal muscle fibers by a denervation atrophy centered on functionality of the neuromuscular junction, both in terms of neuronal plasticity and also especially of trophic influences in neuronal transitions to myofiber contractility. Compensatory synaptic plasticity occurs in muscle and central nervous system of motor neuron disease patients (Pullen and Athanasiou, 2009). Lesion biology is the essential developmental evolution of the dysfunctionality of involvement as systems biology in the first instance.

Complexity: The complexity of expression of the atrophying process is itself symptomatic of the full expressiveness of specific aspects of such developmental evolution. Dysfunctional proinflammatory signalling possibly induces redox-stress secondarily (Carter *et al*., 2009). The broad range of pathologic involvement is indicative of a systems dependency as manifested by the involvement of the motor neuron. Anterograde transport of lysosomes toward synaptic termini might prevent motor neuron degeneration. Mutations in motor proteins possibly lead to neurodegeneration (Lim and Kraut, 2009). The extra-motor involvement of the central nervous system in terms of loss of large myelinated axons and as axonopathy in such organs as sensory nerves and in terms of cognitive decline are indicative of involvement as a pathologic expression of dysfunctional gene expression.

The further evidence that is provided by the progressive muscular atrophies and the inter-relationships of the interactivity borne out by dynamics of progression of the corticospinal tracts and the lower motor neuron show a clearly systematic progression of a biologic lesion of universal applicability in neuronal microenvironmental conditioning. Destabilization and misfolding of mutant forms of superoxide dismutase have been implicated (Wang *et al*., 2009).

Conditioning of systems of dependency in neuronal and skeletal myofiber interactivity would specifically be symptomatic of a synaptic expression of the progression of motor neuron diseases. Amyotrophic lateral sclerosis as involvement of corticospinal tract integrity is particularly illustrative of dynamics of the primary myofiber pathophysiology that evolves especially within contexts of such synaptic involvement. Widespread multi-system involvement tends to develop eventually in long-term sporadic ALS including TDP-43 pathology with ubiquitination (Nishihira *et al*., 2009).

Disease infliction: Degrees of lesion infliction indicate the apparent normality of involvement of the corticospinal tracts in progressive muscular atrophy and as systems of dependency in evolving pathways of connectivity within the central nervous system and at the neuromuscular junction.

Idealization as systems involvement in the first instance might indeed evolve as dying back phenomena of axons and as toxic gain of function of the mutations of the superoxide dismutase gene in cases of some clinical forms of familial amyotrophic lateral sclerosis. The spheroids and neurofilament conglomerates and the specialized selectivity of neurofilament light and heavy chain isoforms might underlie the systematic expression of ubiquitin-positive inclusions in cases of amyotrophic lateral sclerosis. Such developmental biologic expression is symptomatic of a specific involvement that emphasizes dependency of the neuronal-myofiber interactivity as systems integrally evolving also as parallel phenomena of complex identity. Impaired synaptic vesicle release at neuromuscular junctions may contribute to failed postnatal maturation of motor units in spinal muscular atrophy (Kong *et al*., 2009). The further illustrative influences of microenvironmental conditioning might especially indicate the manipulative transformations that developmental identity of the disease biology induces as clinical and pathologic expressiveness.

Genotype influences the distribution of cerebral pathologic features in ALS (Stanton *et al*., 2009). The broad range of pathology of the neuronal-myofiber interactions might be illustrative of a specific dependency of distributional patterns of lesion infliction in motor neuron diseases. Activation of the transcription factor Nrf2 in astrocytes coordinates upregulated antioxidant action and confers protection to nearby neurons (Vargas *et al*., 2008). The bulbar hereditary atrophies and the onset development of disease involvement as early or late-onset disease underlie especially a disease course that occasionally is chronic in only a minor population of the afflicted patients.

The skeins and Bunina inclusions and the ubiquitin-positive inclusions might progressively replace a homeostasis mechanistic system within neurons. Neuronopathy and various involvements primarily affecting either the neuronal cell body or the axon might specifically indicate the essential conditioning of the cells as distributional fields of disease biology and dynamics. Model organisms have contributed to the understanding of complex disease states through analysis of basic cellular processes (Hurt and Silver, 2008). Significance attached to the expression of clinical involvement

illustrates the evolutionary identity of disease biology not only as transformational events but especially as a consequence of mechanistic conditioning of axonal supply of the skeletal myofibers. Mutant SOD1 may be either neuroprotective or cytotoxic depending on its aggregation state (Soo *et al*., 2009).

The integrative identity of the neuromuscular junction in terms not only of synaptic transmission indicates the role of neuronal/myofiber loss of plasticity in the disease biology of motor neuron diseases.

Disturbance in the regulation of splice site selection of protein-coding genes can cause disease (Tazi *et al*., 2009). Neuropathology of corticospinal tracts in relative proportion to loss of Betz cells in the motor cortex and as evidenced loss of neurons in the anterior horns of the spinal gray matter might specifically indicate a progression as systems biology of the broad disease range.

One might conclude that the evolutionary involvement of the nervous system is primarily symptomatic of further progression as evidenced by the clinical muscular involvement. The sparing of diaphragm and accessory muscles of respiration until later stages of the disease indicates that regular activities in axonal trafficking might help prevent in relative fashion the progression of disease involvement.

One might indeed relate the primary bulbar involvement in some cases of motor neuron diseases as a form of disease plasticity in the first instance. Indeed, the disease implicates a variable plasticity potential of the essential disease biology.

Disease evolution: Biology of disease evolution might not simply involve dynamics of transformation of pathologic involvement. The relative interactions of clinical and pathologic involvement might bespeak of the consequential sequence of microenvironmental conditioning arising in connection with disease expression of lesions that are themselves indicative of conditioned loss of plasticity of involvement.

A relative proportionality of involvement as pathologic lesions would consequentially induce loss of plasticity in clinical expression of the motor neuron diseases as further evidenced by systems identity and distributional patterns of progression.

Symptomatic indicators of the conditioning of disease biology are essential manifestations of dynamic interchange as evidenced by distributional patterns of lesion infliction. Post-polio palsy is illustrative of the potential for possible activation of virus infection and as also the instability of the neuronal-myofiber interactivities arising as a consequence of prior poliovirus infection. The involvement in motor neuron diseases might hence progress as increasing instability of neuronal supply of myofibers and especially as loss of plasticity in disease expression.

In terms of lesion identity and infliction, one would consider the biology of involvement of the motor unit as integral mechanics and as further progression of disease activity in the first instance. There is significance in considering the variability of involvement of the motor unit in terms of broad pathologic expression of the motor neuron diseases that are genetically linked. Dynamics of expression and progressiveness of a whole disease category mechanistically transform interactivity as deprivation systems affecting the plastic integrity of the motor unit.

Such motor unit primacy of involvement somehow is expression of the corticospinal tract pathology and as relative to possible additional involvement of the anterior horn spinal neurons.

Developmental biology of disease: Lesions are a represented range of infliction of developmental biology as evidenced by the complex evolutionary course of disease activity. Inherent attributes of progression might help biomark the developmental identity of amyotrophic lateral sclerosis as prototypic expression of the whole category of motor neuron diseases.

In terms of such dynamics of affliction, the biology of systems of progression in expressed motor neuronal lesions would form a basis for categorization of the loss of plasticity in the development of clinical and pathologic microenvironmental conditioning of neurons and of the motor unit.

CONCLUSION

In terms of an equation of balanced integrity and of maintenance of such homeostatic balance, there would appear to evolve a systems biology that centrally implicates the corticospinal tract beyond consideration of morphologic expression of primary lesions within this tract in the first instance.

The expression of such corticospinal tract in terms of the motor unit would further promote a disease progressiveness that is propagated as plasticity and loss of plasticity beyond trophic dynamics of the skeletal myofibers and of the integral motor unit.

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