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Review

Focality, stochasticity and neuroanatomic propagation in ALS pathogenesis☆,☆☆

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ABSTRACT

Amyotrophic lateral sclerosis (ALS) phenotypes such as limb ALS, bulbar ALS, primary lateral sclerosis and primary muscular atrophy are highly heterogeneous and exist on a continuum. These are largely determined by the neuroanatomy of the underlying pathological changes, which can be clinically imputed. Deconstructing these early in disease, before temporal–spatial summation induces complexity, shows that ALS begins focally at a seemingly random location and progresses contiguously. This suggests that focality and anatomic propagation of pathology are significant parts of pathogenesis—disease propagates over space as well as progresses over time. Focality and neuroanatomic propagation can explain how dominant genetic traits manifest with heterogeneous phenotypes, since the anatomic site of outbreak is a prime determinant of phenotype. Focality and neuroanatomic propagation can also explain why frontotemporal dementia (FTD), a neurodegeneration closely related to ALS, has heterogeneous phenotypes, since here too the anatomic site of the outbreak is a prime determinant of phenotype. There are two distinct types of neuroanatomic propagation: contiguous propagation, which occurs side-to-side regionally through the extracellular matrix independent of synaptic connection; and network propagation, which occurs end-to-end dependent on synaptic connections and axonal transmission in connected neuronal networks. The molecular basis of neuroanatomic propagation is unknown, although prion-like misfolding and templating of pathogenic proteins is a compelling unifying hypothesis.

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Abbreviations: ALS, amyotrophic lateral sclerosis; FALS, familial ALS; FTD, frontotemporal dementia; LMN, lower motor neuron; PLS, primary lateral sclerosis; PMA, progressive muscular atrophy; SALS, sporadic ALS; UMN, upper motor neuron.

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ALS phenotype heterogeneity

The phenotypes of amyotrophic lateral sclerosis (ALS) are heterogeneous and complex and complicated nomenclature has evolved to classify them. Typical ALS is characterized by degeneration of upper motor neurons (UMNs) and lower motor neurons (LMNs). Primary lateral sclerosis (PLS) is characterized predominantly by UMN degeneration. Progressive muscular atrophy (PMA) is characterized predominantly by LMN degeneration. Bulbar ALS is characterized by degeneration of motor neurons controlling speech and swallowing. Limb ALS is characterized by predominant degeneration of motor neurons controlling arm and leg function. While these phenotypes seem to be distinctive, in reality, they exist on a continuum. Features that are common to all of them, besides the primary degeneration of motor neurons, are focal initial neuropathology, and progressive contiguous spread. Understanding focality and spread is important to understanding pathogenesis and may provide new ways to approach therapy. This review provides a framework for thinking about this aspect of ALS biology.

Anatomical transparency of the motor system and localizing in vivo neuropathology

Motor neurons are organized anatomically into two tiers, UMNs and LMNs. UMNs are organized somatotopically along the primary motor cortex and span 12 cm from the Sylvian fissure to the cingulate gyrus. Histologically, UMNs are giant Betz cells and pyramidal neurons and reside primarily in cortical layer 5 and project caudally to LMNs. LMNs are organized somatotopically in columns extending from pons to lumbosacral spinal cord over a 55 cm span. Histologically, LMNs consist of alpha motor neurons that reside in Rexed lamina IX of the anterior horns of the spinal cord and in the cranial motor nerve nuclei, and project segmentally out to muscle. Dysfunction of UMNs and LMNs causes characteristic clinical abnormalities that are localizable by physical examination. Dysfunction of UMNs causes slowing and loss of fine skilled movements, spasticity, and hyperreflexia. Dysfunction of LMNs causes weakness, atrophy, fasciculation, flaccidity, and hyporeflexia. The bases for the classification of ALS phenotypes are the clinical exam findings. Several recent clinical studies have deconstructed these and five primary clinical observations may be formulated (Brooks, 1991; Chio et al., 2011; Fujimura-Kiyono et al., 2011; Korner et al., 2011; Ravits et al., 2007b; Turner et al., 2010).

Five observations of ALS motor phenotypes

Focal and random onset

The first observation is that initial symptoms appear focally at probably random regions of the body. They may appear in bulbar muscles such as masticatory, facial, pharyngeal, tongue, or laryngeal muscles; in limb muscles such as shoulder, forearm, hand, thigh, knees or foot muscles; or in axial or respiratory muscles. When ALS begins in the limbs, where detection may be lateralized, deficits typically are unilateral. These observations suggest that at the onset of disease, the pathological process that underlies clinical symptoms is focal and stochastically (randomly) located in the nervous system.

Propagation by contiguous spread

The second observation is that disease progresses by contiguity. This is shown in two ways. First, the motor dysfunction in a focal body region where symptoms first appear becomes progressively worse in this same region over time, slight at first and then steadily worse. Second, the motor dysfunction spreads outward to contiguous regions, progressing for example, from one side of the body to the other or from one region to the next. This suggests that the underlying pathology is propagating neuroanatomically, starting discretely within an area of the neuraxis and then spreading to contiguous regions.

UMN and LMN convergence

The third observation is that while initial symptoms appear in focal body regions such as the head, arm, trunk, or leg, both UMN and LMN signs are maximal in the same region. It may be predominately at the UMN level (lateral, mid or medial cortical convexity) or predominantly at the LMN level (for example pons, medulla, C5, C8, L4 or L5), or a combination. But, importantly, the focal body area where symptoms first appear is the area that has maximal UMN and LMN degeneration. This suggests that at the onset of disease, UMN, LMN and peripheral muscle degenerations are connected, not independent, and that the trigger has set off disease that is distributed within a UMN–LMN-muscle network.

UMN and LMN independence

The fourth observation is that after disease is triggered and begins spreading contiguously, the spread is independent at the UMN and LMN levels. This is best seen when onset of symptoms is in an arm. LMN clinical deficits progress from one arm to the other, consistent with neuronal anatomy of LMNs in the spinal cord. UMN clinical deficits, by contrast, progress from arm to ipsilateral leg, consistent with the somatotopic anatomy of the cerebral cortex. Because of differences between UMN and LMN somatotopic anatomies and spread distances, initial signs of degeneration that are seen in one body region progress differently between the UMN and LMN levels to other body regions over time and motor manifestations become increasingly complex. Said differently, the outward progression in the body of UMN and LMN degenerations are incongruous and this creates increasing complexity of phenotypes over time. This desynchronization with spread suggests degeneration proceeds independently at UMN and LMN levels.

Kinetics of propagation

The fifth observation is that rates of clinical progression are determined by the kinetics of propagation. While the phenotypes are largely determined by the anatomy of underlying degeneration, the rates of progression are largely determined by the overall kinetics (Fujimura-Kiyono et al., 2011). Most studies of progression rates measure overall functional deficits and do not analyze regional progression nor independently measure UMN and LMN progression. Detailed studies of overall progression by Munsat et al. in the 1970's and 1980's showed rates of decline in different body regions (Andres et al., 1987; Munsat et al., 1988). Important questions are whether progression is similar at the UMN and LMN levels, and whether overall progression is a summation between them. PLS and PMA, which are the extremes where the pathological burden is predominantly at one level, generally have better prognoses than ALS, perhaps attributable to this fact that disease is primarily at one level rather than two.

Focality, stochasticity and neuroanatomic propagation

The above observations are idealizations and simplifications of what is clearly complex, but they point to the formulation that focal and random initiation of pathology and subsequent spread contribute significantly to ALS biology (Ravits and La Spada, 2009). Critical in this are: (1) focal onset of pathology in the nervous system leading to focal outbreak of symptoms in a somatic region; (2) random location of this in the neuraxis and hence a random location of symptoms in the body; (3) involvement at onset of connected UMNs and LMNs innervating this peripheral somatic muscle and hence simultaneous and congruous UMN and LMN symptoms at the time disease is triggered; and (4) outward propagation of the pathology independently at UMN and LMN levels according to somatotopic anatomy and hence spreading