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Contextual Developmental History of Evolving Global and Focal Parameters in Multiple Sclerosis Progression

Lawrence M. Agius
Department of Pathology, Mater Dei Hospital, Tal-Qroqq, Medical School,
University of Malta, Msida, Malta, Europe

Abstract: Dimensional confines of the individual demyelinating plaque in multiple sclerosis indicate a focal or multifocal involvement of the parent axon and also a global progressiveness of the involvement of the blood-brain barrier. A gliopathy affecting viability of the astrocytic foot processes may be re-interpreted within constructs of involvement by a depleted oligodendroglial cell compartment within the demyelinating plaque. It is particularly significant to view dynamics of remyelination within a contextual setting of an afflicted parent axon. Progressiveness is hence compounded by multiple constructs in development of a lesion that is physico-chemically related to new foci of involvement of grey and white matter, beyond the confines of established plaque pathology. In this sense, therefore, a conventional role for a presumed viral etiology would insufficiently account for a multi-focal involvement that mirrors the global dimensions of the blood-brain barrier defects.

Key words: Inflammation, multiple sclerosis, plaque, demyelination, blood-brain barrier

INTRODUCTION

Overall dimensions of involvement of the central nervous system in inflammatory demyelinating disorders is a correlative and systematic study in the evolutionary loss of the structured composition of the myelin sheath as this specifically contributes, in turn to degrees of loss of axonal integrity. Genetic susceptibility is a most significant contributor to multiple sclerosis pathogenesis (Goodin, 2009). The significance of pathology of the blood-brain barrier in neuro-myelitis optica is illustrative of the significant contribution of blood flow dynamics and also of possible hypoxia (Trapp and Stys, 2009) in lesion infliction affecting the myelin sheath of individual axons. Enhanced expression of vascular endothelial growth factor is associated with demyelinating plaques in both multiple sclerosis and experimental encephalomyelitis (Roscoe *et al*., 2009).

In spite of the focal and multifocal distribution of the demyelinating plaques in multiple sclerosis, it is the overall complexity of involvement (Palace, 2009) of the white and grey matter of the central nervous system that primarily characterizes pathogenesis, including the infectious background of the disease (Krone *et al*., 2009).

This involvement is significantly modified by dynamics of pathology of the blood brain barrier, particularly in terms of the injury to the abluminal aspect of blood vessels in relation to the astrocytic foot processes or astrocytic limitans in specific relation to blood flow dynamics.

DEVELOPMENT OF DEMYELINATION

The actual demyelinating process is relative to the onset and further contributing roles of various factors that disrupt the composition of myelin in terms relative to physico-chemical reconstruction around axons. Patients with severe presentation and poor recovery continue on a similar trajectory in subsequent attacks (Mowry *et al*., 2009).

The terms of reference with regard to the antigenic epitope unmasking subsequent to such demyelinating events are indicative of a series of lesion inflictions contributing to transection of the parent axons.

In such context, the axon is the original focus of involvement in demyelination in a serial continuum of further lesion inflictions related to disruption of the blood-brain barrier.

Leukocyte migration into the central nervous system is mediated by chemokines expressed on endothelial cells (Subileau *et al*., 2009).

Remyelination in particular is a significant correlative process in the development of systems of demyelination in the first instance.

Corresponding Author: Lawrence M. Agius, 27 Ballarat, Guzeppe Caruana Str., Tal-virtu, Rabat RBT09, Malta Europe

The role of the injured parent axon in stages of reattempted remyelination is significant in particular reference to the development of the autoimmune attack as demyelinating waves of recurrent disease that characterize in particular the relapsing-remitting form of multiple sclerosis.

The various aspects of dynamic involvement of the myelin sheath are a complex series of interactions that complicate the development of further promoted attempts at reconstruction of the integrative functionality of the parent axon.

One might view the different aspects of evolution of the demyelinating plaques as these reflect in variable manner the dynamics of pathologic involvement of the blood brain barrier.

It is the overall dimensional involvement as relative to either partly or un-preserved integrity of the blood-brain barrier that dominantly characterizes in secondary fashion the sequential processes leading to repeated demyelination of the parent axons within the multiple sclerosis plaque.

PARENT AXONS

Parent axons are, centrally operative factor in the contributing developmental process of demyelination as a defective series of evolutionary steps in further production of lesions related to permeability defects affecting capillaries and post-capillary venules (Zivadinov and Minagar, 2009).

The failed attempts at successful and sustained maintenance of the myelin sheath are significant in reference to the redefined dimensional involvement of the blood-brain barrier.

In this sense, the biologic involvement of the parent neuron would constitute an initial focus of involvement by pathologic lesions that secondarily involve the myelin sheath. Remyelinating attempts at reconstruction of the axon-myelin-sheath structural complex are reflected constructs in the evolutionary course of lesions primarily affecting the parent axon in the first instance. Axonal injury may result from chronic toxic demyelination in spite of remyelination (Lindner *et al*., 2009). In this manner, a sequential evolution in development of the demyelinating plaque is one constructed around the parent axon as relative proportional dynamics arise in terms of a defective blood-brain barrier, including also possible association with Epstein-Barr virus (Gutierrez *et al*., 2008).

COMPLEXITY OF INVOLVEMENT

The full complexity of involvement as pathogenesis of the biologic lesions of demyelinating plaques is developmentally determined by a series of injuries that originates as a focus of persistent activity in the parent axonal compartment.

The relative contributions of T-cell subtypes ($CD8^+$ suppressor and $CD4^+$ helper) (Weiner, 2009) and of a humoral-complement pathway would illustrate the developmental dimensions of a demyelinating process that is remitting-relapsing or monophasic in certain cases of multiple sclerosis. The heterogeneous nature of human B lymphocytes indicates diversity of function and implied roles in autoimmune disease such as multiple sclerosis (Anolik *et al*., 2009).

The relative terms of association of a severe attack of demyelination with often a monophasic clinical course of the multiple sclerosis process would indicate a constructive validity in significant reference to the defects of the blood-brain barrier as originally inflicted at the early stages of presentation of the multiple sclerosis process in that individual patient.

The initial involvement by the multiple sclerosis disease process is one related to a significant correlation biologically and pathogenetically between the parent axon and the blood-brain barrier. In such a setting of dynamic disequilibrium in relative proportion between lesions in the parent axon and the defects in the blood-brain barrier, there would subsequently evolve a series of demyelinating and alternating remyelinating events within constructs of the multiple sclerosis plaque (Korn, 2008).

OPERATIVE CONSTRUCTS OF INJURY

A physico-chemical dimension of operative constructs in the development of multiple sclerosis plaques is indicative of the focality of involvement of the parent axon and of the dimensional globality of the pathologic defects affecting the blood-brain barrier in patients undergoing a remitting-relapsing clinical course.

In terms of development, the demyelinating plaque that might significantly illustrate dynamics of evolution in the myelin degradation, it is particularly interesting to note the role of proteases (Roycik *et al*., 2009) as disease activity markers that is essentially secondary to pathology dually arising in the parent axon and in the blood-brain barrier.

In terms of origin of such dual pathology, a systemic form of involvement that globally envelopes both axons and blood vessels might significantly contribute in particular to a glial pathology that further compromises integrity of both astrocytes and oligodendrocytes (Cercignani *et al*., 2009).

In reference to such pathology of the glial compartment of the nervous system, the dynamics of

infliction of the astrocytes and oligodendrocytes might relate to the undifferentiated roles of astrocytes relative to the differentiated oligodendrocytes. It is significant that astrocytes appear to functionally correlate as essentially undifferentiated oligodendrocytes in the first instance. The differentiation process of oligodendrocyte progenitor cells is however poorly understood (Mi *et al*., 2009).

NEURODEGENERATIVE CONSTRUCT

The positional prominence of the neurodegenerative construct as parent axonal involvement would centrally evolve in terms of subsequent glial involvement affecting especially the astrocytic foot-processes as these defectively implicate the global dimensional parameters of the blood-brain barrier.

In this sense, a composite reconstruction of dynamics of interchange between the parent axon and myelin sheath within the demyelinating plaque would correlate with a defective blood-brain barrier in a manner that specifically activates immune attack on the myelin sheath. Neurotrophic factors may induce neuro-protective autoimmunity and modulate immune responses as well as target tissue susceptibility (Linker *et al*., 2009).

In this sense, the complex interactions of various principal component systems with the cellular and extracellular compartments would further illustrate the acquisition of new pathogenic factors that are sequentially recruited in further damaging the myelin and other components of the multiple sclerosis plaque, including astrocytic necrosis by anti-aquaporin-4 antibody-positive serum (Kinoshita *et al*., 2009).

GLOBAL DIMENSIONS IN MULTIPLE SCLEROSIS

Global dimensions of involvement assume the focal reconstructive dynamics of the remyelinating axon in terms that inherently implicate the neuronal interactivity with the glial compartments of the central nervous system.

Myelin modulates immune cell adhesion and mobility (Pool *et al*., 2009). The precise mode of development of lesions as well-defined multiple sclerosis plaques would appear a correlative construct in the evolutionary activation of injurious agents that variably afflict the parent axonal compartment. Neurodegeneration is a significantly contributing component in a setting of a globally defective blood-brain barrier in further development of the dimensional involvement by the multiple sclerosis plaque. The overall dimensions of progression as multiple individual plaques distributed both within white and grey matter would implicate in particular the glial compartment as a predilected site of pathologic dynamics of disease evolution. Grey matter volume loss is associated in multiple sclerosis with focal atrophy in deep grey nuclei and also with diffuse atrophy of the cerebral cortex (Grassiot *et al*., 2009).

PARTICIPATING ROLES IN PATHOGENESIS

The complexity in participation of injury as a cellular compartment upset in homeostatic maintenance would indicate the developmental dimensions of a disease process based on the relative contributions of an essentially secondary immune component as autoimmune attack of the myelin sheath.

The oligodendrocyte may not be the exclusive target of multiple sclerosis pathology (Bishop *et al*., 2009). Parent axonal components are significantly correlated with a neurodegenerative process that sequentially involves the parent axon within contextual confines of multiple focal demyelinating plaques. Endocannabinoids are implicated both in neurodevelopment and neurodegeneration (Basavarajappa *et al*., 2009).

Evidence that neuroinflammatory infiltrates significantly contribute within systems of immune-mediated attack to the myelin sheath might signify the relative proportionality of developmental evolution of lesions primarily involving the parent axon. Mitochondrial alterations with energy failure are implicated in axonal degeneration in multiple sclerosis (Mahad *et al*., 2009).

The conventionally recognized patho-physiologic roles of viral infectious agents insufficiently account for the unfolding dynamics of evolution of multiple sclerosis as a global disease process that manifestly progresses as multiple focal multiple sclerosis plaques (Frykholm, 2009).

NEURO-INFLAMMATION

The generic nature of the neuroinflammation in multiple sclerosis clearly contributes to the participant roles of various proteases in destroying the extracellular matrix and also the basal lamina of capillaries supplying the focal regions of involvement in multiple sclerosis.

Further pronounced interactivity would significantly contribute to dimensional reconstruction as repeated episodes of attempted remyelination of the parent axon. Extensive remyelination contributes to functional recovery (Duncan *et al*., 2009). The interactions between individual parent axons within the demyelinating plaque would contribute to a focality of involvement that illustratively progresses within contextual dynamics of involvement of the glial cell pathology.

The defective blood-brain barrier would hence constitute the referential context of involvement of multiple cellular compartments, including a macrophage/ microglial series of system pathways.

The origins of the neuroinflammatory pathways are significant contributors to the final endpathway reactivity as constituted by an immune attack on the myelin sheath. Neuroinflammatory activity is closely associated with all lesions and disease stages of multiple sclerosis (Frischer *et al*., 2009).

The remitting-relapsing nature of the demyelinating plaque would materially contribute to the development of recurrent phases in evolution of both cellular and humoral immune responsiveness.

The universal applicability of multiple pathways in pathogenic developmental history of the demyelinating plaques would resolve in terms of a focal involvement by a globally progressive defect of the blood-brain barrier. Also, matrix metalloproteinase-7 facilitates immune access or restimulation in perivascular regions in multiple sclerosis (Buhler *et al*., 2009).

It is within such contextual construction of injury to both neurons and glia that the neuroinflammatory reactivity originates as further injury-inducing agent and as activator of the immune response towards the myelin sheath.

The role of the neuro-myelitis optica immunoglobulin-G (Watanabe *et al*., 2009) that reacts with the aquaporin-4 would certainly reflect a multiplicity of lesion inflictions within the focal multiple sclerosis plaque confines.

CONCLUSION

The background activity of the multiple sclerosis plaque milieu proves a conducive set of circumstances that promotes progressiveness of disease activity as evidenced by repeated episodes of demyelination and possibly also synaptic degeneration (Centonze *et al*., 2009). The agencies responsible for demyelination would also contribute materially to the onset of multiple attempts at remyelination of an injured parent axon (Stangel, 2008). It is in this sense that the neurodegeneration of the individual axons is parent contributor to a disease process that eventually depletes the oligodendroglial cell components within the demyelinating plaques.

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