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Multiple Sclerosis Is A Neurodegeneration Specifically Targeting Oligodendrocytes and Myelin Sheaths

Lawrence, M. Agius
Department of Pathology, St Luke's Hospital, Gwardamangia
University of Malta Medical School, Msida, Malta, Europe

Abstract: Considerations regarding pathogenesis of multiple sclerosis plaques would revolve around heterogeneous modes of involvement of a central venule in the ongoing progression of relapsing/remitting demyelination and of axonal loss. Neurodegeneration of the parent neuron appears pivotal as a demyelinating /remyelinating series of events borne out by the inflammatory nature of the lesions, the multiple sclerosis plaques. Implied involvement of inflammatory and immune cell elements might help account for modes of progression of an ischemic lesion that targets the oligodendrocyte with loss of its myelin sheath around multiple independent segments of an integral axon. Indeed, multiple sclerosis proves a neurodegenerative state that progresses as a demyelination of segmental axonal involvement and of individual oligodendrocytes around specific venules of supply.

Key word: Neurodegeneration, sclerosis, oligodendrocytes

INTRODUCATION

MULTIPLE SCLEROSIS IS A HETEROGENEOUS DISORDER

Multiple sclerosis implicates a heterogeneous pathology that evolves both as plaques and also as a global meningoencephalomyelitis. It is in terms of such inflammatory activity that microglia and CD4+T lymphocytes promote a progressive demyelination as a parametric function of axonal injury[1,2] Axons develop features of transection and other evidence of neurodegeneration that involve subsequent recurrent demyelination. Remyelination of such injured axonal segments might help account for various attributes of a disease process that promotes progression clinically both as a relapsing/remitting condition and also as an acute and chronic evolution of plaques that enlarge and progressively lose myelin and oligodendrocytes [3].

A close pathologic correlation of the endothelium with oligodendrocyte injury and loss might develop as a complex interplay of immune reactivity to reactivated Major Histocompatibility Class II antigens on macrophages[4]. Inflammatory injury to axonal segments [5] might imply a progression of such injury that permits pathologic correlation of endothelial cell loss with oligodendrocyte cell loss, both concurrent with demyelination and remyelination cycles of activity.

Endothelial cell damage would imply a variability of disease outcome arising as a heterogeneity of involvement of segments of the axon as variable parameters of disease activity.

Segmental axonal involvement is invariably a neurodegenerative process that progresses via demyelination and remyelination of multiple axons and of multiple axonal segments[6]. It might be reasonable to consider how invariably progressive multiple sclerosis degeneration is one related closely to loss of oligodendrocytes and to a progressive plaque gliosis in relative proportion to lack of trophic factor support. Ciliary neurotrophic factor may act as an effective neuroprotective mechanism against neurodgeneration in multiple sclerosis[7]. Immunomodulatory roles for Th2 and Th1 T helper lymphocyte subset would allow for a progression that cyclically compounds and self-amplifies injury to a demyelinating and remyelinating axonal segment.

Remyelination of axonal segments might constitute a true form of injury in its own right related inherently to increased susceptibility of the supplying oligodendrocyte[8] and as a reflection of progressive gliosis of the multiple sclerosis plaque.

Plaque enlargement is a phenomenon of progression beyond simple considerations of increased oligodendrocyte loss but more related to an endothelial cell injury reflecting a breakdown of the blood brain barrier. It might be significant to consider plaque gliosis a reparative response to such endothelial cell injury irrespective of the actual degree of oligodendrocyte cell loss.

Antigen presentation only allows a certain permitted degree of reactivity to injury as the segmental axon evolves as a focus of inflammatory injury.

Corresponding Author: Lawrence, M. Agius, 27 Guzeppi Caruana Street Tal-Virtu, Rabat, RBT 09 Malta, Europe

Biomarkers for axonal degeneration in multiple sclerosis include neurofilament light chain in cerebrospinal fluid whereas antibodies against the heavy chain isoform are associated with disease progression[9] .

Integrins on T lymphocytes might function as a correlated system closely monitoring blood brain barrier breakdown with progressive loss of myelin that alternates inherently with remyelinating cycles.

It might be significant to consider all aspects of a multiple sclerosis process that are progressive and invariably independent of demyelination as either a primary pathogenetic event or as a secondary phenomenon to segmental axonal injury or inflammation[10]. A decrease in the levels of plasma membrane calcium ATPase isoform 2 that extrudes calcium from neurons enhances neurodegeneration in experimental allergic encephalomyelitis[11].

Remyelination accompanies axonal injury and allows progression of cyclical MS disease activity in promoting further evolution to a fully mature plaque.

Only in such terms can one both realize a phenomenon of plaque generation and determine progression as a process of involved participation of injury to endothelial cells and to oligodendrocytes.

REMYELINATION AS DYNAMIC PROGRESSION IN MULTIPLE SCLEROSIS PLAQUES

The MS plaque constitutes in a sense a realized outcome for pathway activity involving modes of inflammatory involvement of myelinated axons[12]. A basic concept of reactivity to axonal injury might help account for reparative events as myelination and demyelination, in response to axonal injury and repair. Mitochondrial mechanisms may contribute to neurodegeneration. Genetic variants of Complex 1 genes influence tissue response to neuroinflammation[13] .

Demyelination is a singular type of evolved effect that allows cell- and antibody- mediated injury to resolve as an expanding multiple sclerosis plaque. It might be reasonable to consider how axons are transected early in the course of a meningoencephalomyelitis in terms particularly of modes of directed response to injury or repair of tissues.

The enhancing effects of Interferon gamma on ischemia-induced neurotoxicity may be implicated in multiple sclerosis, particularly as a synergistic mechanism with Tumor Necrosis Factor[14] .

Reparative tissue events resolve as gliotic scars in the form of sclerotic plaques that are burnt-out foci of oligodendrocyte lysis and of demyelination. Indeed, demyelination and oligodendrocyte cell loss would constitute an effective endresult to modes of involvement of inflammatory reactivity implicating immunobiologic rejection of antigenic determinants as exposed by repeated demyelination and remyelination of axonal segments.

Vascular endothelial pathology as an inflammatory reactivity to injury might prove distinct from a basic concept of infectivity borne out by a virus in a general setting of encephalitis. It might be instructive to consider endothelial cell responsiveness as reparative gliosis and as repeated attempts at remyelination of axonal segments irrespective of actual dynamics of demyelination or even of axonal transection.

A mechanistically, partly resolving, reparative pathway might help account for a remyelination that modulates axonal injury[15] .

Remyelination appears integral to disease pathogenesis in multiple sclerosis that allows participation of various reactive cellular and molecular species in tissue injury. Nitric oxide and its toxic metabolite peroxynitrite in particular may inhibit mitochondrial components of the respiratory chain and induce neurodegeneration and neuroinflammation as seen in Multiple Sclerosis[16] .

Neurodegeneration as a definite stage in resolved plaque activity in MS patients would be suggestive of attempted reparative events in remyelination that predetermine dynamics of active demyelination of axonal segments[17] .

Recovery from a relapse would involve remitting injury of axonal segments that are often partially or completely transected and also demyelinated. Resolution of a demyelination event as a primary axonal injury would account for variable response to various potentially injurious agents that include ischemia, infection and inflammation, especially in response to hypervascularization and gliosis, involving cytokines such as Tumor Necrosis Factor-alpha and Interferon gamma[18] .

Axonal segmentation would be suggestive of a inflammatory response that transforms reactive injury to reparative remyelination.

Calcium influx via voltage gated calcium channels appears significant in inducing axonal injury in experimental allergic encephalomyelitis and multiple sclerosis[19] .

Resolving or resolved reparative events might account for mechanistic pathways that implicate variable remyelination of axons transected at an early stage in the inflammatory response phase of MS plaque expansion.

Cyclical remyelination might prove effective mechanistic progression of a segmental axonal injury

arising within a context of ongoing demyelination and transection of inflamed axons.

Multiple sclerosis involves the genesis of well-defined plaques that further enhance distinctive margin demarcation from surrounding apparently normal white matter. The presence of inflammation in surrounding white matter would correspond to a series of evolved phenomena linked to genesis of the plaques and to their progressive expansion.

Staged evolution in disease pathogenesis might implicate plaque definition closely reflecting progressiveness of the disease process[20]. A three-dimensional constructive evolution of the plaque might implicate a perivenular distribution of multiple different cellular species with dynamic transfer between the intravascular and extravascular compartments. Vasculogenesis appears a driving influence in expansion of an MS lesion that transforms to a well-demarcated plaque only in terms of the normal appearing but inflamed white matter. Vascular endothelial reactivity and vasculogenesis would perhaps induce plaque formation that sharply self-demarcates from surrounding white matter in terms of several cellular and reactive chemical species.

CYCLICAL REMYELINATION AND DEMYELINATION IN AXONAL INJURY

Multiple sclerosis constitutes a persistent stimulus for remyelination that however varies in degree of effectiveness. Such a reparative response would arise largely as a result of hereditary attributes determining both oligodendrocyte and axonal integrity rather than in terms of severity of immune reactivity[21] . Delayed remyelination appears particularly prone to the evolution of a largely demyelinated MS plaque that chronically expands. Axonal injury may prove a predominant determinant for remyelination in such chronically demyelinated MS plaques[22].

Demyelination and remyelination may constitute variable effectiveness in inducing progression of an axonal pathology or permanent axonal loss in MS patients.

A concept of neurodegenerative progression as a component endstage lesion in multiple sclerosis might account for variable responsiveness as remyelination or demyelination of initially injured axons.

MOLECULAR OR ENSHEATHMENT DEGENERACY OF THE MYELIN AROUND AXONAL SEGMENTS IN MS PROGRESSION

Degenerated myelin would stimulate a directed immunological response as demyelination of multiple sclerosis type, implicating particularly progressive myelin sheath injury[23] .

One might indicate the evolution of myelin sheath loss that progresses as neuroinflammation and as inflammation-induced myelin loss.

Autoimmune response appears a primarily reinstituted injury based on progression of a specific degeneration of the myelin sheath[24] as also reflected in the subsequent relapsing/remitting course of the MS disorder. T lymphocytes and antibody-mediated myelin sheath injury might specifically correspond to either a predetermined form of degeneration to myelin structure or to a corresponding rearrangement of the myelin sheath itself with respect to its enwrappment around the axon. A high degree of T-cell receptor degeneracy and molecular mimicry appear frequently implicated in initiation of the autoimmune response in multiple sclerosis[25] .

COMBINED OLIGODENDROCYTE AND MYELIN SHEATH INJURY AS ISCHEMIALLY CONDITIONED PLAQUE GENESIS

Variable shifts in monocyte influx into MS lesions might account for variable chemokine receptor expression based particularly on an ischemic component in lesion progression[26] . Ischemic genesis of MS plaques appears intrinsically a process of induced involvement of the oligodendrocyte that self-perpetuates as relapsing demyelination of axonal segments. One might perhaps consider how inflammatory chemokines would promote selectivity for monocyte or microglial cell participation in a context of evolving ischemic injury to oligodendrocytes.

Ischemia perhaps evolves as a pathogenic factor in inducing susceptibility in progression of lesions ranging from an oligodendrocytopathy to a more directly evolving demyelination affecting multiple axonal segments around an axial vessel of supply as plaques distributed within an inflamed white matter.

Attributes of such a possible ischemic event constituted as a series of progressive steps in injury inflicted on oligodendrocytes might account for variable cellular inflammatory response as the disease proves either acute or chronically progressive.

MS plaque genesis may prove an expressed form of ischemic injury implicating combined dynamics of oligodendrocyte loss and of injury to the myelin sheath around a pathologic blood supply pattern.

Only in terms of understanding such a relationship between injury and response of a combined injury to oligodendrocytes and myelin sheath would there emerge a clear concept of dynamics of progressive loss of axonal integrity in the eventually chronically mature MS plaque.

INTERACTIVE RESPONSE TO INJURED OLIGODENDROCYTES AND MYELIN SHEATHS

A proinflammatory microenvironment appears to result from ongoing events in multiple sclerosis pathogenesis linked inherently to how astrocytes interact with microglia and macrophages, on the one hand, and with injured oligodendrocytes, on the other[27] .

One might view aspects of ongoing neuroinflammation as simply events that derive their progressiveness from ongoing injury to cellular constituents, particularly oligodendrocytes. In terms beyond simple delineation of cellular injury and of cellular responsiveness, chemokine availability and receptivity might constitute active markers of progression of a process; such a process would implicate pathogenesis linked to microglia and macrophages and to different modes of possible injury to the oligodendrocyte and its myelin sheath.

SEPARATE, INDIVIDUAL AXONAL SEGMENTS IN MS PATHOPHYSIOLOGY AND PROGRESSION

Neurotrophic signaling appears to comprise processes of stabilization or progression of a channelopathy as represented by Na v1.8 in Purkinje neurons in experimental allergic encephalomyelitis or multiple sclerosis[28] . Ongoing events clinically and pathophysiologically in MS might reflect fundamental attributes of a process of injury ranging in scope from oligodendrocyte cell death to neurodegeneration within the integral context of active demyelination of separate, individual segments of axon.

PATTERNED ANATOMY OF DEMYELINATION IN MULTIPLE SCLEROSIS

A distinct predilection for subpial cortical distribution of MS plaques appears to arise as a phenomenon favoring onset and progression of patterned injury to myelin sheaths[29] .

It would appear that anatomical considerations predetermine susceptibility to demyelination in a manner that might implicate regional variability of response of oligodendrocytes to standardized forms of injury ranging from viral infection to neuroinflammation to ischemia. Neurotrophic factor biology[30] appears a probable protagonist in such a scenario involving an irreversibility of response once injury to the myelin sheath is initiated and becomes established.

OLIGODENDROCYTE CELL INJURY IS THE TARGET LESION IN MS PLAQUE GENESIS

Vascular endothelial growth factor (VEGF) appears to constitute a pivotal mechanism in the evolution of the neuroinflammatory lesions[31] . Modes of interaction between monocytes/macrophages and CD4+ and CD8+ T lymphocytes may be central to development of a concurrent series of vascular responses inducing inflammation. Injury to oligodendrocytes, and dynamics of such cellular injury, would participate in different ways whereby monocytes/macrophages stimulate the immune system to possible viral antigen determinants.

VEGF in turn would dominantly and selectively determine modes of evolution of injury to the oligodendrocyte as a largely neuroinflammatory mode of inflicted transformation of blood brain barrier hyperpermeability. Considerations of vascular hyperpermeability might clearly delineate modes of involvement of the injury to oligodendrocytes that are directly reflected in loss of myelin sheaths.

It is only in terms of such injury to the oligodendrocytes that subsequent relapses and remissions in myelination of axons eventually result in the burnt-out MS plaques of chronic endstage disease.

AUTOCRINE-INDUCED INJURY TO END OTHELIAL CELLS IN MS WHITE MATTER

Endothelial-cell tight junctions would correlate with a system of injury to vessels primarily characterized by progressive transformation of normal white matter to the MS plaque[32] .

Even normal appearing white matter may constitute, in MS patients, a mode of autocrine potentiation of amplified injury to endothelial cell tight junctions.

Interferon beta constitutes modes of integration of endothelial cell functionality that approximate normal anatomical and morphologic constitution of the endothelial cell bed. Realization of an endothelial cell bed that progressively transforms in terms particularly of autocrine-induced injury to the endothelial tight junctions might very well represent a progression-determining element dominantly characterizing multiple sclerosis as mainly a relapsing/remitting condition of classic type.

VCAM-1 DEFINES SUSCEPTIBILITY TO ONSET OF MS DISEASE INVOLVEMENT

Direct interaction between microglia and oligodendrocytes might evolve in terms of how adhesion molecules themselves determine and indeed potentiate such interactions[33] .

Potentiation of microglially-induced cell death of oligodendrocytes would perhaps constitute expressed modes of development of the neuroinflammatory state that would affect potential multiple sclerosis patients. Indeed, a selectivity in responsive participation of microglia that in turn express vascular endothelial adhesion molecule-1 would predetermine the establishment of a chronically relapsing remitting multiple sclerosis disease course that is definable both clinically and pathologically.

ACTIVE NEURODEGENERATION CAUSES BOTH DEMYELINATION AND SUBSEQUENT AXONAL LOSS IN MULTIPLE SCLEROSIS

Axonal injury would range from an inflammatory axonopathy to an actively progressive neurodegeneration linked inherently to demyelination and to subcellular organelle injury[34]. One might speak of how relapsing remitting disease becomes established as a chronically progressive disorder largely in terms of how such subcellular organelle injury leads to axonal loss of neurodegenerative type.

Axons form larger swellings or spheroids in multiple sclerosis and also in traumatic brain injury. These are terminal endbulbs of axon stumps and may implicate a common mechanism in many different CNS disease states[35].

A scheme of reproducible injury to axons that is manifested mainly by an initial demyelinating series of relapses and remissions might evolve largely in terms of axonal tracts that deplete mechanisms of possible recovery on the part of partly injured or actively degenerating neurons.

It might be significant to consider an actively evolving injury as a neurodegeneration of the parent neuron that presents initially as demyelination and subsequently as axonal loss affecting that particular neuron.

APOPTOSIS AND ANTI-APOPTOSIS OF INFLAMMATORY CELLS IN MS PLAQUE ACTIVITY

Protective neurotrophic effect in multiple sclerosis appears operative in terms of both glial and inflammatory cell reactivity implicating in turn microglia/macrophage infiltration of the whole of the chronically active MS plaque[36] . Apoptotic and anti-apoptotic signals would alternatively influence reactivity of MS plaques to a series of inflammatory cell infiltrates that are sustained or suppressed by NGF production of autocrine/paracrine glial and inflammatory cell systems.

One might speak of how inflammatory cell infiltration of the chronically active MS plaque induces an autoimmune reactivity that is influenced in a specifically modulated fashion by Nerve Growth Factor.

FOCAL LESION INDUCTION IN MS PLAQUE FORMATION

Activated autoimmune response to a focal lesion in the CNS appears a uniformly operative system of stimulation of various inflammatory and immune responses implicated in multiple sclerosis[37] . A focal lesion induced by viral infection, trauma or ischemia would constitute a series of events that transform the potential variability of response of inflammatory and immune cells to an ongoing or persistently relapsing form of disease activity characteristic of multiple sclerosis. One might speak of how the immune response is itself a stimulated effect of mechanistic inflammatory activity related to an injury that primarily arises focally in the CNS.

Focal responsiveness to injury of the CNS would evolve largely in terms of how such injury is a predeterminant in transforming evolution of the MS plaque.

AN INFLAMMATORY AND IMMUNE RESPONSE DUE TO AXONAL INVOLVEMENT IN MS

Determination of axonal injury in chronic viral infection of neurons might specifically implicate an accentuation of the chronic inflammation that secondarily induces an immune response[38] .

In terms of such axonal injury, one might specifically consider how compromised axonal integrity promotes the perpetuation of repeated relapses of demyelination as seen in many patients suffering from multiple sclerosis[39]

A clear delineation of events linked to development of multiple sclerosis plaques might specifically implicate a progressiveness of response and a transformation series of pathways. Impaired fibrinolysis in particular may potentially contribute to axonal damage in multiple sclerosis[40] . The latter would convert the focal lesion of injury to one of relapsing/remitting type and the subsequent evolution to a chronically progressive plaque. Plaque evolution would specifically implicate a variability of outcome based largely on interactivity of inflammatory and immune cells that repeatedly induce demyelination of axonal segments that develops immune responsiveness to a possibly virally infected neuronal cell body.

REPEATED DEMYELINATION DEPLETES RECOVERABILITY FROM AXONOPATHY IN MULTIPLE SCLEROSIS

Axonal dysfunction would constitute a widespread lesion of the normally appearing white matter in patients suffering from multiple sclerosis[41,42] .

Delineation of such axonal dysfunction from a disruptive lesion affecting axonal continuity within the multiple sclerosis plaque might perhaps depend on how lesions in themselves constitute a realized pathway of evolution of various forms of injury that transcend simple considerations of either dysfunction or even of axonal transection[43]. The naked axon appears more susceptible to further injury[44] .

A revised scheme of inflammatory axonopathy in multiple sclerosis would revolve around dynamics of demyelination that would either accentuate the effects of expression of the axonopathy or else transform such axonopathy to an established pathway of progressive injury to the rest of the neuron.

Neuronal cell body injury would acquire dimensions of progression linked inherently to modes of participation of axonal and dendritic processes and of a demyelination that progressively depletes recoverability from such axonopathy.

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