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A Regional Basis for Multiple Sclerosis Demyelination in Vascular Plaque Cores

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Abstract: Multiple sclerosis plaques constitute distinctive lesions of disease involvement evolving largely as extension of margins and also as new foci in other regions of the white matter. It appears that a vascular basis for progression would also implicate a series of axonal lesions that incorporate demyelination as aggregate phenomena affecting both oligodendrocytes and neurons. A strict neuronopathy and an axonal participation in the loss of myelin sheaths in multiple sclerosis might evolve as immunologically mediated processes arising on vessels and endothelium within plaques that enlarge and subsequently mature. In terms of such demyelination of multiple plaques there would subsequently evolve a process of repeated remyelination of the axonal segments largely based on a phenomenon of aggregate involvement of multiple oligodendrocytes supplying multiple segments of different axons on a regional basis of progression.

Key words: Multiple sclerosis, demyelination, plaques

INTRODUCTION

GROUP AGGREGATES OF OLIGODENDROCYTE INVOLVEMENT OCCUR ON A VASCULAR BASIS OF THE INDIVIDUAL MS PLAQUE

Multiple Sclerosis (MS) occurs as an overall progressive disorder inherently arising as plaques of demyelination that enlarge progressively[1]. The three dimensional evolution of MS plaques would involve an epicenter constituting axial reference points particularly to such progressive enlargement. One might speak of vascular cores to MS plaques constituted particularly by venules with inflammatory mediators released into the immediately adjacent white matter. Interactions of CNS endothelial cells with vascular basement membrane extracellular matrix form part of the cellular immune response in MS[2]. Vascular and neuropil components would evolve in terms of a white matter that accounts for much of the clinicopathologic impact of the constitutive disease process. Extracellular matrix proteoglycan alterations are temporarily dynamic and widespread and may be critical to lesion pathogenesis in MS patients[3]. It is only in such terms that one might correlate T lymphocyte reactivity targeting myelin sheaths investing individual axonal cylinders with progressive waves of recurrent demyelination of the enlarging MS plaque.

Myelination and remyelination would constitute modes of interactivity arising as a series of events based on an inflammatory process of vascular participation.

It may furthermore appear that modes of involvement of the oligodendrocyte and of the axon are simply components of an overall process that is global but that exhibits itself as multiple demyelinating plaques. Interface reactivity of oligodendrocytes with a myelin sheath that promotes axonal pathology might progress as a demyelinating wave of axonal deterioration[4].

Even in terms of myelin sheaths that are distinct from the axon itself yet

clearly a subcomponent of pathologic involvement of such axon, whole plaques of individually progressive demyelination of the axon would involve oligodendrocytes on an aggregate rather than individual basis. Both pro- and anti-apoptotic mechanisms are activated within and outside of the MS plaques[5].

Group oligodendrocyte pathology would perhaps relate particularly to the vascular cores of individual plaques rather than to enwrapped axons. Increased numbers of proliferating oligodendrocytes are found in most MS plaques regardless of disease duration[6].

Ovoid plaques constitute not only a central core of pathologic progression[7] but also, in a special sense, systems of progression in terms of enlargement of foci of white matter demyelination. Indeed, demyelinating waves might be defined as axonal loss that peripherally is modified to a pure myelin sheath loss. Axonal loss is widespread in MS and its extent is tract specific and size selective[8].

In an analogous manner, atherosclerotic plaques

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would appear also centered on the subintima or intima whereby progressive ulceration and thrombus encrustation are general complications in the enlargement of plaques.

Indeed, one might view whole systems of ischemia and hypoxia in conjunction with a central series of damaging events involving the endothelium as contributing to ulceration of vascular wall infarction.

Ischemic-like involvement of white matter without actual infarction of tissues would perhaps constitute modes of presentation with loss of myelin sheaths and a subsequent tendency for axonal degeneration progressing as the enlarging MS plaque. In fact, marked trophy of brain and spinal cord detected by volumetric quantitation correlates with neurological disability[9].

Delineation of margins of MS plaques as a transition to or from a demyelinating state may implicate an MS process developing as loss of viability of axons and reflecting oligodendroglial degeneration.

VASCULAR POTENTIATION OF NEUROINFLAMMATION IN MULTIPLE SCLEROSIS PLAQUES OF DEMYELINATION

Vascular compromise of the white matter would complicate an MS process that initially develops as inflammatory involvement of blood vessels and subsequently progresses as loss of myelin sheaths. Early axonal damage may be at least partly reversible[10].

Demyelinating plaques in MS may relate often to characteristic sites of predilection involving angles of ventricles and floor of the fourth ventricle together with frequent involvement of optic nerves and spinal cord.

Biology of blood supply of myelin sheaths would appear allied to pathology progressing as initially impaired delivery of certain vitamins or essential nutrients. In MS, also, blood-brain barrier hyperpermeability is associated with lesion pathogenesis linked to pathology in microvascular tight junctions[11].

Segmental demyelination of peripheral nerves in diabetics, the loss of myelin of the dorsal spinal columns in vitamin B12 deficiency and the demyelination of the corpus callosum in alcoholics in Macchiafava Bignami disease may constitute allied representative pathways of myelin loss.

In view of the dynamics of progressively severe loss of myelin in delineated plaques in MS patients, the attributes of neuroinflammation in these patients are an essential deterioration of blood supply to multiple focally delineated regions of the white matter. Inflammation is accompanied by altered local cerebral perfusion that precedes plaque development in multiple sclerosis and prior to permeability of the blood brain barrier[12].

Predilection for central nervous system myelin in multiple sclerosis would correlate with characteristics of a blood supply pattern that involves cerebral white matter affecting oligodendrocytes that enwrap multiple axons.

The axon-myelin sheath unit might characterize a dependence of oligodendrocytes on viability of an axonal blood supply. The peak of relapses in MS coincides with severe inflammation and demyelination and axonal pathology correlates with clinical progression. Axonal damage is evident from earlier stages and increases in severity with subsequent relapses in an MS experimental model[13].

A heterogeneity of pathways in inflammatory progression in patients with demyelinating plaques would perhaps underscore variability of parameters of a disease that arises initially as damage to either endothelium or intima of vessel walls, especially venules, in white matter. Also, macrophages may exert deleterious effects on the stem cell population in neuroinflammatory disorders[14].

The oligoclonal bands of immunoglobulin in the cerebrospinal fluid appear a responsive element that implicates antigenic modification of myelin determinants in the immune response of MS patients. An exogenous agent may contribute to such specific antigenic determinations in delineating subsequent transformations in immune sheath enwrappment of axons in white matter.

In terms of leptomeningeal blood vessels, progression in MS is a vascularity-based phenomenon. Blood flow dynamics of variable stasis or of turbulence might participate in vascular wall impermeability that is specifically pro-inflammatory.

Replicative capability and oligodendrocyte viability and recoverability after injury would perhaps affect loss of myelin sheaths as severe demyelination of the MS plaques.

The actual demyelinating event might complicate immunological involvement of blood vessels that promotes myelin breakdown without necessarily implicating immunologically targeted oligodendrocytes. CD83-positive dendritic cells are present in perivascular cuffs in MS lesions and may originate in the peripheral circulation as monocytes[15]. The proteolipid composition of myelin would perhaps constitute a sequence of progression that is inherently demyelinating when inflammation is centered on blood vessels supplying plaques.

A proinflammatory involvement of white matter venules constitutes an antigenic characterization of endothelial cells that would tend to self-progress as compromised white matter viability.

The actual release and deposition of myelin proteolipid would excite a macrophage response that is specifically proinflammatory in its own right. Such a phenomenon would feed a cyclical turnover of macrophages as well as of lymphocytes that further contributes to myelin breakdown and release. The blood-brain barrier is disrupted by activated T cells of non-neural specificity and allows large plaque-like regions of demyelination to form in the presence of circulating anti-myelin antibody[16].

Cyclical lymphocytic turnover might provide a pathobiologic basis for progression in multiple sclerosis in terms particularly of proinflammation initiation that is transformed to progressive demyelination of the MS plaque. Also, there is evidence of abnormal ubiquination of axons in the surrounding normally myelinated white matter in the brain of MS patients[17].

Endothelial participation in the ongoing neuroinflammation might promote the introduction of various agents contributing to eventual plaque enlargement.

Lymphocytic homing to MS plaques would appear an endothelial characterization with breakdown of myelin proteolipid. A delineation of cycling activity of lymphocytes may transcend simple homing dynamics in the ensuing repeated waves of plaque neuroinflammation. A CNS-targeted antigen-driven response appears present in MS plaques[18].

The clinical manifestations in multiple sclerosis would arise due to loss of axonal functionality and viability. Disease cycles of activity would progressively increase in severity as demyelinating plaques enlarge.

In the burnt-out plaque there is diminution of neuroinflammation as related to blood vessel pathology and to myelin lipid loss.

Lymphocytic percolation of the vascular wall would constitute a means of access of neuropil and myelin sheaths. Extensive involvement of plaques may develop as interactivity of lymphocytes and macrophages with axonal loss an additional factor in disease progression. Axonal viability is lost and contributes to loss of the myelin sheath in MS plaques.

Lymphocytes as endothelially transformed antigenic reactivity to the myelin sheath would allow cycling of the lymphocytes in relapses and remissions of the disease.

Transmigration of lymphocytes through the vessel wall might active cycling of homing lymphocytes. Vascular wall reactivity might augment homing of lymphocytes as a recycling of antigenic determinants particularly on the endothelial cells. In vascular compromise, cycling and recycling of lymphocytes would induce macrophages to break down myelin sheaths and to enlarge and delineate the MS plaque.

Immune privilege of the central nervous system would characterize blood vessel interacting with myelin sheaths would lead to removal of the myelin and enlargement of the MS plaque. The MS plaque is a phenomenon of flux and demyelination arises as a series of changes in antigenic characterization. Targeting of the myelin sheath would lead to amplification of the immune response in forming multiple MS demyelinating plaques.

DEMYELINATION IS A FORM OF AXONAL INJURY AND REMYELINATION AS REACTIVE TO SUCH AXONAL INJURY

A multiphasic course involving the regeneration of myelin might evolve in the multiple sclerosis patient that is linked to antibody production and to CD4+/CD8+ T lymphocyte reactivity. Even in terms of how myelin regenerates in relative proportion to damage to the myelin, it is perhaps relevant to consider death of oligodendrocytes a phenomenon that is primarily regional. Such regionality of involvement of oligodendrocyte pathology might actually evolve both as a cause and paradoxically also as a consequence of a series of changes affecting the deposition pattern of regenerating myelin.

In this sense, scars of demyelination might develop largely as dynamic and post-dynamic evolution of primarily and secondarily regenerating myelin sheaths. The strict regionality of evolving myelin damage would inherently arise from repeated episodes of a multiphasic regenerative phenomenon starting and progressing largely as secondarily evoked reactivity reflected especially in antibody and T-cell responsiveness[19].

The actual regeneration of myelin appears largely regional in terms not only of evolving injury to the myelin sheaths but particularly also of an acute axonal injury that progresses both as a decrease in diameter of axons and also as a decrease of axonal density.

Such myelin regeneration that is associated with acute axonal injury would tend to subsequently evolve as a multiphasic subacute or chronic process that is regional.

Extension of axonal injury into adjacent white matter appears to correlate with a global process of secondary damage progressing largely as axon/myelin inter- reactivity.

A myelin regenerative wave in response to an acute axonal injury may account for a strict regionality in multiphasic evolution of repeated episodes of myelin regeneration and of axonal loss.

Demyelinating injury of axons constitutes an axonal damage in its own right primarily determines dynamics of the demyelination and remyelination.

An intrathecal oligoclonality in antibody production in multiple sclerosis would correlate with multiphasic antibody production[20] that disrupts axon-myelin inter-reactivity in inducing further axonal injury. Myelin loss linked inherently to further attempts at myelin regeneration might prove central to evolving axonal injury.

Heterogeneity in clinical presentation of multiple sclerosis patients relates to differentially expressed dynamics of onset and progression of a disease process that varies largely with loss of myelin sheaths but also with progression of the remyelination progression.

Myelin regeneration predetermine dynamics of occurrence and progression of demyelinating episodes. Acute inflammatory activity involves a full range of progressiveness of any single episode of regional demyelination. Modes of involvement of disease are predetermined by parameters governing acute development of inflammation reactions in foci of demyelination in individual MS plaques.

Regional inflammation in MS plaques would involve a variability of response even in terms of remyelination of the lost myelin sheaths. Myelin loss and regeneration simply reflect a disorder that primarily injures the axon through loss of its myelin sheath. Alterations of neuronal components of the central nervous system play a role in MS[21].

DOES DEMYELINATION POTENTIATE POSSIBLE SUBSEQUENT DYSMYELINATION DEFECTS THROUGH A PRIMARY NEURONOPATHY?

A glial-neuronal participation as cooperative factors in the development of demyelination might incorporate both an astrocytic interaction with oligodendrocytes and a neuronal involvement of axonal interactions with a variety of cell types including oligodendrocytes and astrocytes. Axonal contribution to progression and to recurrence of multiple sclerosis lesions might specifically implicate modes of interaction of neurons with astrocytes as induced by neurotransmitter-related toxicity.

A primary neuronopathy may be significant in the precipitation of lesions affecting, secondarily, interactions between the axon and its myelin sheath. An axon is injured as an inherent component of each episode of demyelination in active multiple sclerosis plaques.

Astrocytes would appear a source of progressive injury implicating both a primary neuronopathy and also an oligodendrocytic involvement as demyelination of multiple sclerosis type.

The propensity for repeated remyelination after each demyelinating episode in the multiple sclerosis plaque would redefine the MS plaque as a focus of concomitant involvement of neuronal and glial cells inducing myelin restructuring around segments of multiple adjacent axons.

Dysmyelination as in the Pelizaeus-Meizbacher disease is accompanied by an element of hypomyelination that progresses with disease involvement of the axon. Such episodes of decreased myelination are associated with a myelin restructuring that progresses particularly as increased gene dose or as deficient gene dose related to proteolipid protein expression and synthesis. Quantitative rather than gross qualitative differences in gene expression pattern may define the progression from acute to chronic active plaques in MS[22]. On the other hand, actual demyelination appears a significant pathogenetic component in progression of the metabolic leukodystrophies and of Alexander's leukodystrophy associated with dysfunctional activity as represented by mitochondrial disorders. A mitochondrial mechanism of tissue loss is possibly implicated in MS[23].

A combination of dysmyelination with demyelination in some leukodystrophies would be suggestive of a demyelinating episode progressing as a definitive restructuring of myelin sheaths around axons and as a further reflection of previously incompletely expressed genetic defect in myelin component synthesis.

Hypomyelination, demyelination and dysmyelination appear to constitute differential expressions of a neuronopathy that primarily affect the onset of abnormal myelination linked to a progressive axonal pathology that affects the myelination process

NEURONAL PRECIPITATION oF DEMYELINATION IN MS

Neuronal apoptosis correlates with demyelination in multiple sclerosis that arises in a context of induced amplified neuroinflammation. Such induced neuroinflammation progresses largely as a demyelination specifically inducing injury and possibly also apoptosis of cells. Indeed, in terms of an evolving inflammatory reactivity, neuronal body loss appears an essential component of multiple sclerosis that acutely promotes injury to axonal segments.

Persistent complement activation in large MS lesions

may also lead to death of oligodendroglia with permanent axonal damage[24].

Axonal transections induce neuroinflammatory injury that progresses largely as involved neuronal cell body rather than of the ensheathing myelin layers. Neuronal apoptosis proves a determinant of progressiveness of a multiple sclerosis process, once this is initiated.

Decreased ATP synthesis with CNS inflammation can ultimately lead to cell death or degeneration[25].

An injury to the neuronal cell body may lead to a disease process that damages both the myelin sheath and its enwrapped axon. Indeed, various cytokine/chemokine mediators in multiple sclerosis would appear to be produced by neurons and related microglia that further orchestrate ongoing waves of neuroinflammatory activity.

Precipitation of waves of demyelination would induce progression linked intrinsically to neuronal injury. Anti-DNA antibodies are a major component of the intrathecal B cell response in MS and may promote important neuropathologic mechanisms in these patients[26].

Modes of amplified neuroinflammation inducing injury may affect different components of the neuron.

Neuronal apoptosis correlates with concurrent myelin loss of multiple segments of any one axon. Oligodendrocyte cell body lysis is also a mechanism of progressive injury in multiple sclerosis.

Hence, a multiplicity of initiated pathways of induced injury to the neuronal-axonal-oligodendrocyte-myelin sheath unit would correlate with a progressive MS process initiated and progressing in terms of primary and secondary waves of neuroinflammation[27].

Autoimmune responsiveness would induce injury in multiple sclerosis that propagates further damage to myelin and axon. There is in situ evidence for antibody- and complement- mediated demyelination in MS plaques that results in incomplete loss of oligodendrocytes and their reappearance with remyelination[28].

It is only with reference to the neuronal cell body, on the one hand and of the oligodendrocyte cell body, on the other, that one might account for a disease process that is either progressive or relapsing-remitting in clinical course, but one eventually spreading in the central nervous system beyond confines of the plaque.

IS PLAQUE GLIOSIS A STRICT CORRELATE OF DEMYELINATION AS ASSOCIATED WITH AXONAL INJURY ANDNEURONAL APOPTOSIS?

Multiplicity of lesions that are heterogeneously distributed within gray [29] and white matter would reflect an ongoing disease process that progresses uniformly in a given patient. Heterogeneous modes of involvement of different patients might implicate a reactivity arising in terms of onset and progression of different cascade pathways inducing demyelination[30].

Secondary demyelination might well define variable initiation of events as evolving pathology of white matter in particular.

Primary events that secondarily induce loss of myelin as MS plaques would perhaps induce reactive progression of axonal induction of demyelination.

Strictly segmental demyelination of the axon would correlate with suboptimal maintenance of the lipid layers that progress in terms of subsequent injury to the axonal segment.

Distinct margins to the MS plaque relate to advancing reactive demyelination that induces concurrent astrocytic proliferation. Gliosis in a demyelinative plaque is recognizable as primary and secondary events in such demyelination. The demyelinating process appears a primarily episodic event that correlates with an ongoing gliosis of the MS plaque concurrent with ongoing cascade pathways that progress. Pathways of initial involvement in MS plaque generation lead eventually to the mature and burnt-out chronic plaque with complete demyelination[31]. Ongoing gliosis in the MS plaque correlates with activity in the individual MS plaque concerned. In later stages of gliosis, the perfusion decreases with increasing axonal injury[32].

Demyelination and gliosis progress hand in hand with enlargement of the plaque and would perhaps implicate axonal pathology ranging from the demyelinative event itself to actual transection and loss of segments of axon. Multiple dispersed lesions would progress as various endpathways ranging from loss of myelin to apoptosis of involved neurons. Such progression would implicate axonal transection that induces apoptosis of the neuronal body together with cascade pathways of demyelination and possibly oxidative damage to DNA in MS plaques[33].

Multiple lesions induce the initiation of an injury that specifically progresses from demyelination to axonal transection as progressive gliosis further depletes myelin sheaths in the plaque region.

REFERENCES

1. Keeley, S.M., Y. Kim and J.M. Provenzale, 2004. Redefinition of multiple sclerosis plaque size using diffusion tensor MRI. AJR, Am. J. Roentgenol., 183: 497-503.
2. Sobel, RA., 2001. The extracellular matrix in multiple sclerosis: An update. Braz. J. Med. Biol. Res., 34: 603-609.

3. Sobel, R.A. and A.S. Ahmed, 2001. White matter extracellular matrix chondroitin sulfate/dermatan sulfate proteoglycans in multiple sclerosis. J. Neuropathol Exp. Neurol., 60: 1198-1207.
4. Raine, C.S., 1997. The Norton Lecture: A review of the oligodendrocyte in the multiple sclerosis lesion. J. Neuroimmunol., 77: 135-152.
5. Banisor, I. and B. Kalman, 2004. Bcl-2 and its homologues in the brain of patients with multiple sclerosis Mult. Scler., 10: 176-181.
6. Solanky, M., Y. Maeda, X. Ming and W. Husar *et al.*, 2001. Proliferating oligodendrocytes are present in both active and chronic inactive multiple sclerosis plaques. J. Neurosci. Res., 65: 308-317.
7. Poser, C.M. and V.V. Brinar, 2004. The nature of multiple sclerosis. Clin. Neurol. Neurosurg., 106: 159-171.
8. DeLuca, G.C., G.C. Ebers and M.M. Esiri, 2004. Axonal loss in multiple sclerosis: a pathological survey of the corticospinal and sensory tracts. Brain, 127: 1009-1018.
9. Ukkonen, M., P. Dastider, T. Heinonen, E. Laasonen nad E. Elovaara, 2003. Volumetric quantitation by MRI in primary progressive multiple sclerosis: volumes of plaques and atrophy correlated with neurological disability. Eur. J. Neurol., 10: 663-669.
10. Mancardi, G., B. Hart, L. Roccatagliata and H. Brok *et al.*, 2001. Demyelination and axonal damage in a non-human primate model of multiple sclerosis. J. Neurol Sci., 184: 41-49.
11. J. Kirk, J. Plumb, M. Mirakhur and S. McQuaid, 2003. Tight junctional abnormality in multiple sclerosis white matter affects all calibers of vessel and is associated with blood brain barrier leakage and active demyelination. J. Pathol., 201: 319-327.
12. Wuerfel, J., J. Bellmann-Strobl, P. Brunecker and O. Aktas *et al.*, 2004. Changes in cerebral perfusion precede plaque formation in multiple sclerosis: A longitudinal perfusion MRI study. Brain., 127: 111-119.
13. Onuki, M., M.M. Ayers, C.C. Bernard and J.M. Orian, 2001. Axonal degeneration is an early pathological feature in autoimmune-mediated demyelination in mice. Microsc Res. Tech., 52:731-739.
14. Brundin, L., H. Brismar, A.I. Danilov, T. Olsson and C.B. Johansson, 2003. Neural stem cells: a potential source for remyelination in neuroinflammatory disease. Brain Pathol., 13: 322-328.
15. Plumb, J., M.A. Armstrong, M. Duddy, M. Mirakhur and S. McQuaid, 2003. CD83-positive dendritic cells are present in occasional perivascular cuffs in multiple sclerosis lesions. Mult. Scler., 9: 142-147.
16. Westland, K.W., J.D. Pollard, S. Sander, J.G. Bonner, C. Linington and J.G. McLeod, 1999. Activated non-neural specific T cells open the blood-brain barrier to circulating antibodies. Brain., 122: 1283-1291.
17. Giordana, M.T., P. Richiardi, E. Trevisan, A. Baghi and L. Palmucci, 2002. Abnormal ubiquination of axons in normally myelinated white matter in multiple sclerosis brain. Neuropathol Appl. Neurobiol., 28: 35-41.
18. Owens, G.P., M.P. Burgoon, J. Anthony, B.K. Kleinschmidt-DeMasters and D.H. Gilden, 2001. The immunoglobulin G heavy chain repertoire in multiple sclerosis plaques is distinct from the heavy chain repertoire in peripheral blood lymphocytes. Clin. Immunol., 98: 258-263.
19. Gilden, D.H., M.P. Burgoon, B.K. Kleinschmidt-DeMasters and R.A. Williamson *et al.*, 2001. Molecular immunologic strategies to identify antigens and b-cell responses unique to multiple sclerosis. Arch. Neurol., 58: 43-48.
20 Qin, Y., P. Duquette, 2003. B-cell immunity in MS) Int. MS J., 10: 110-120.
21. Caramia, M.D., M.G. Palmeri, M.T. Desiatoand Boffa L *et al.*, 2004. Brain excitability changes in the relapsing and remitting phases of multiple sclerosis: a study with transcranial magnetic stimulation Clin. Neurophysiol., 115: 956-965.
22. Tajouri, L., A.S. Mellick, k.J. Ashto and A.E. Tannenberg AE *et al.*, 2003. Quantitative and qualitative changes in gene expression patterns characterize the activity of plaques in multiple sclerosis. Brain Res. Mol. Brain. Res. Nov., 119: 170-183.
23. Kalman, B. and T.P. Leist, 2003. A mitochondrial component of neurodegeneration in multiple sclerosis. Neuromolecular Med., 3: 322-328.
24. Schwab, C. And P.L. McGeer, 2002. Complement activated C4d immunoreactive oligodendrocytes delineate small cortical plaques in multiple sclerosis. Exp. Neurol., 174: 81-88.
25. Lu, F., M. Selak, J. O'Connor and S. Croul *et al.*, 2000. Oxidative damage to mitochondrial DNA and activity of mitochondrial enzymes in chronic active lesions of multiple sclerosis. J. Neurol Sci., 177: 95-103.
26. Williamson, R.A., M.P. Burgoon, G.P. Owens and O. Ghausi *et al.*, 2001. Anti-DNA antibodies are a major component of the intrathecal B cell response in multiple sclerosis. Proc. Natl. Acad. Sci. USA., 98: 1793-1798.

27. Lucchinetti, C.F., W. Brueck, M. Rodriguez and Lassmann, 1998. Multiple sclerosis: lessons from neuropathology. Semin. Neurol., 18: 337-349.
28. Storch, M.K., S. Piddlesden, M. Haltia, M. Iivanainen, P. Morgan and H. Lassmann, 1998. Multiple sclerosis: in situ evidence for antibody and complement-mediated demyelination. Ann. Neurol., 43: 465-471.
29. Babshi, R., S. Ariyaratana, R.H. Benedict and L. Jacobs, 2001. Fluid-attenuated inversion recovery magnetic resonance imaging detects cortical and juxtacortical multiple sclerosis lesions. Arch. Neurol., 58:742-748.
30. Wingerchuk, D.M., C.F. Lucchinett and J.H. Noseworthy, 2001. Multiple sclerosis: Current pathophysiological concepts. Lab. Invest., 81: 263-281.
31. Poser, C.M., 2000. The pathogenesis of multiple sclerosis: a commentary. Clin. Neurol Neurosurg. 102: 191-194.
32. Haselhorst, R., L. Kappos, D. Bilecen and K. Scheffler *et al*., 2000. Dynamic susceptibility contrast MR imaging of plaque development in multiple sclerosis: application of an extended blood-brain barrier leakage correction. J. Magn. Reson. Imaging., 11: 495-505.
33. Vladimirova, O., J. O'Connor, A. Cahill, H. Alde, C. Butunoi and B. Kalman, 1998. Oxidative damage to DNA in plaques of MS brains. Mult. Scler., 4: 413-418.