The Pathogenesis Of Primary Progressive Multiple Sclerosis: Antibody-Mediated Attack And No Repair?

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Abstract

Primary progressive multiple sclerosis (MS) differs from the more common form of MS which has an initial relapsing–remitting course in a number of ways, including pathological features, clinical course, differential diagnosis and response to treatment. The lesions in primary progressive MS tend to be more diffuse, less inflammatory and less likely to remyelinate than those occurring in relapsing–remitting MS and secondary progressive MS; there are also fewer focal lesions in the brain in primary progressive MS. Recent evidence suggests that antibodies to central nervous system (CNS) antigens have an important role in disease progression. Such antibodies could cause demyelination, inhibit remyelination and cause axonal destruction. Ongoing immune attack by autoantibody and lack of CNS repair could be responsible for the gradually increasing disability in primary progressive MS. Further research on the B-cell and autoantibody response in primary progressive MS might lead to advances in diagnosis and treatment. Inhibition of autoantibody production by inducing B-cell apoptosis with rituximab is a potential new therapy for primary progressive MS.

Keywords: antibodies; autoimmunity; B cell; multiple sclerosis; rituximab; T cell

Introduction

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS) that almost certainly has an autoimmune basis. Most patients with MS have an initial relapsing–remitting course with attacks of neurological impairment followed by clinical recovery and intervals without deterioration. The majority of patients with an initial relapsing–remitting course eventually enter a phase of progressive clinical deterioration with or without superimposed relapses (secondary progressive MS). Some people with MS have progressive clinical deterioration from onset (primary progressive MS); most of these patients do not experience relapses but 28% have a relapse at some stage.[1] Primary progressive MS differs from relapsing–remitting and secondary progressive MS not only in clinical course but also in pathological features, differential diagnosis and response to treatment. This review will focus on the pathogenesis of primary progressive MS and its implications for understanding and improving diagnosis and treatment.

Clinical Features And Diagnosis Of Primary Progressive Ms

Primary progressive MS tends to have a later age of clinical onset (mean ~39 years), typically about 10 years later, than relapsing–remitting MS.[1,2] Interestingly, a recent case report of the clinical presentation of primary progressive MS 10 years after the incidental finding of typical magnetic resonance imaging (MRI) brain lesions raises the possibility that the CNS lesions may actually have a similar age of onset as in relapsing–remitting MS.[3] The female to male ratio in primary progressive MS (1.3:1.0) is lower than in relapsing–remitting MS.[1,2] Progressive paraparesis is the most common presentation of primary progressive MS;[4] progressive visual loss may be the presenting feature but is uncommon.[2,5,6] Irreversible disability occurs sooner after clinical onset in primary progressive MS than in patients with an initial relapsing–remitting course.[7] In contrast, once irreversible disability occurs, the time course of progressive disability is similar in primary progressive and secondary progressive MS.[7]

Primary progressive MS is more difficult to diagnose than relapsing–remitting MS for the following reasons: (1) in contrast to the relapsing–remitting pattern which occurs in few neurological diseases other than MS, the progressive neurological deterioration over months and years that occurs in

primary progressive MS is also typical of many other neurological diseases; (2) the variety of neurological symptoms and signs occurring in primary progressive MS tends to be more limited than in relapsing–remitting MS, and this also reduces the distinctiveness of the clinical features; (3) there are fewer MRI focal brain lesions [8, 9] and less frequent gadolinium-enhancing brain lesions[10] in primary progressive MS than in relapsing–remitting / secondary progressive MS; and (4) oligoclonal immunoglobulin (Ig) bands restricted to the cerebrospinal fluid (CSF) occur less frequently in male patients with a later onset and progressive myelopathy,[11] that is the type of patient likely to have primary progressive MS. New diagnostic criteria have recently been proposed for definite primary progressive MS;[12, 13] however, the absolute requirement for evidence of intrathecal IgG synthesis will significantly reduce the diagnostic sensitivity.

Genetics Of Primary Progressive Ms
There is an increased occurrence of other autoimmune diseases in patients with MS and in their first-degree relatives, suggesting that individuals with MS have a genetic predisposition to autoimmunity in general.[14] This applies at least as often to patients with primary progressive MS as to those with relapsing–remitting or secondary progressive MS.[14] It has been hypothesized that this genetic susceptibility results in a failure of activation-induced apoptosis of autoreactive T lymphocytes in the CNS [15] because these T cells receive survival signals from B lymphocytes harbouring the Epstein–Barr virus.[16] Different class II major histocompatibility complex (MHC) genes are associated with different autoimmune diseases, probably because they determine which self antigens and therefore which organs are targeted. MS is associated with the HLA-DRB1*1501-DQA1*0102-DQB1*0602 haplotype. [17] This haplotype occurs at a similar frequency in primary progressive MS, relapsing–remitting MS and secondary progressive MS; however, patients with primary progressive MS are more likely to have a DR6 haplotype combined with this haplotype.[18] Such a difference in MHC expression could result in different CNS antigens being targeted by the immune system and consequent differences in CNS repair and disease progression. Other genes may also influence the course of MS by exerting a modulatory effect on the immune response. A recent study found that a particular polymorphism of the cytotoxic T-lymphocyte antigen 4 (CTLA4) gene, which downregulates T-cell function, is associated with primary progressive MS.[19]

Possible Mechanisms Of Relapse And Progression
A relapse differs from progression in that the clinical deterioration during a relapse is usually more rapid, of limited duration and reversible, whereas the clinical deterioration during progression is slower, prolonged or indefinite, and not reversible. The degree of neurological impairment is the outcome of a dynamic relationship between immune attack on the nervous system and repair of the nervous system.

Relapse
Relapses are likely to be due to episodes of immune attack on CNS myelin by T cells with or without antibody, followed by remyelination leading to repair and clinical recovery. In chronic relapsing experimental autoimmune encephalomyelitis (EAE), an animal model of MS, relapses are characterized by inflammatory cell infiltration and primary demyelination, whereas remissions are characterized by resolution of inflammation and by remyelination. [20] Clinical relapses of MS are associated with an increase in the number and extent of gadolinium-enhancing lesions,[21] which correlate with perivascular inflammation.[22] Patients with relapsing–remitting MS have surges of increased numbers of circulating myelin-reactive T lymphocytes which partly correlate with the number of gadolinium-enhancing brain lesions.[23] Thus, attacks of MS might be due to episodes of T cell attack on CNS myelin. The presence of antimyelin antibody will increase the extent of demyelination and the severity of the neurological deficit, as it does in EAE.[24] The combination of T cells and antibody is commonly present in active demyelinating lesions in MS.[25] Remyelination occurs in the CNS in MS[26] and is likely to contribute to clinical recovery, as it does in EAE.[27]

Progression
Progression of neurological impairment could be due to two mechanisms. First, it could be due to a rapid and relentless immune attack on CNS myelin and axons by T cells and antibody; this might be the mechanism in the rarely occurring acute MS (Marburg's disease) and will not be discussed further. Second, it could be due to a prolonged slow immune attack on myelin and axons without CNS repair; this might be the mechanism in primary and secondary progressive MS. A prolonged slow immune attack on the CNS is more likely to occur when antibodies, rather than T cells, constitute the main mechanism of attack because circulating antigen-specific antibody levels remain persistently elevated as opposed to the marked

fluctuations that occur in the levels of circulating antigen-specific T cells. A failure of CNS repair could occur because of immune attack preventing remyelination or because of immune-mediated destruction of axons, which cannot regenerate in the human CNS. Antibodies are more likely than T cells to be effective inhibitors of remyelination because of their persistence and ability to spread diffusely through the CNS parenchyma. Thus, progression in primary and secondary progressive MS might be due to a predominantly antibody-mediated immune attack that causes demyelination and inhibits remyelination or that causes axonal destruction. Relapses superimposed on a primary progressive course might be due to episodes of T-cell immune attack on the CNS with or without CNS repair.

Pathogenesis Of Primary Progressive MS

Inflammation

Gadolinium-enhancing MRI brain lesions occur much less frequently in primary progressive MS than in secondary progressive MS10 and relapsing–remitting MS,[21] indicating that there is less inflammation in the brain in primary progressive MS. Histological studies have shown less perivascular lymphocytic cuffing and parenchymal inflammatory cell infiltration in the CNS in primary progressive MS than in secondary progressive MS.[28] Immunological studies have shown increased blood T-cell reactivity to the 184–209 region of myelin proteolipid protein in relapsing–remitting MS and secondary progressive MS, but not in primary progressive MS,[29] although T-cell reactivity to the gangliosides GM3 and GQ1b is increased in primary progressive MS.[30] Furthermore, blood leukocyte expression of adhesion molecules, which have a role in the trafficking of circulating leukocytes into the CNS, is different between primary progressive MS and relapsing– remitting/secondary progressive MS.[31]

Antibody

Recent evidence indicates that an increased CSF B cell to monocyte ratio correlates with disease progression in MS [32] and that the presence of intrathecal IgM synthesis in relapsing–remitting MS predicts secondary progression.[33] These findings raise the possibility that disease progression is related to antibody-mediated CNS damage. Patients with primary progressive MS have increased serum antiganglioside antibody levels compared to those with relapsing–remitting MS and controls; [34, 35] the levels in secondary progressive MS tend to be intermediate between those in primary progressive MS and relapsing–remitting MS.[35] Furthermore, antibodies to light neurofilament subunit, an axonal cytoskeletal protein, are increased in the CSF in primary and secondary progressive MS compared to relapsing–remitting MS.[36] Antibodies to CNS antigens could contribute to progression by causing demyelination or axonal damage or by inhibiting remyelination. Further definition of these antibodies might lead to advances in the diagnosis and prognosis of primary progressive MS.

Neuronal damage

Hypointense lesions ('black holes') on T1-weighted MRI brain imaging correlate with severe tissue destruction, including axonal loss, [37] and their rate of accumulation correlates with rate of disease progression in secondary progressive MS.[38] However, hypointense T1 brain lesions occur much less frequently in primary progressive MS than in secondary progressive MS and no more frequently than in relapsing–remitting MS.[39] Furthermore, histological studies indicate that acute axonal injury occurs less frequently in the focal lesions of primary progressive MS and relapsing–remitting MS than in the focal lesions of secondary progressive MS.[40] Therefore, if axonal damage has a major role in causing neurological impairment in primary progressive MS, it might be occurring diffusely rather than focally. Although the total brain white matter focal lesion load is considerably lower in primary progressive MS than in secondary progressive MS,[8, 39] diffuse lesions on T2-weighted and proton density-weighted imaging occur more commonly in the brain and spinal cord in primary progressive MS than in secondary progressive MS.[39] Furthermore, magnetization transfer imaging in primary progressive MS has revealed the presence of diffuse tissue damage undetectable by conventional MRI, the extent of which matches that of patients with secondary progressive MS with similar levels of disability.[41] The contribution of cerebral cortical damage to neurological impairment in MS also needs to be considered. Conventional MRI is insensitive for detecting cortical lesions but automated analysis has shown cerebral cortical atrophy in primary progressive MS despite minimal white matter lesion accumulation.[42] Cerebral cortical lesions in MS are characterized by demyelination, axonal transection, dendritic transection, neuronal apoptosis and reduced inflammation compared to white matter lesions.[43] It remains to be determined to what extent cerebral cortical damage contributes to disease progression in primary progressive MS.

Remyelination

Demyelinated lesions without oligodendrocyte recruitment or remyelination occur more frequently in primary progressive MS than in relapsing–remitting MS and secondary progressive MS.[44] In three cases of primary progressive MS, the demyelination in such lesions has been associated with oligodendrocyte death in a small rim of periplaque white matter, adjacent to the zone of active myelin destruction.[25] The lack of remyelination raises the possibility that immune attack might prevent remyelination in primary progressive MS and that demyelination without remyelination could be an important mechanism for disease progression. One possible immune mechanism for inhibiting remyelination is the action of antiGM3 antibodies which are elevated in the sera of patients with primary progressive MS;[35] these antibodies might interfere with the important role that GM3 ganglioside has in the differentiation of oligodendrocyte progenitors toward myelin production.[45]

Spinal cord involvement

Whereas the MRI focal lesion load in the brain in primary progressive MS is lower than in relapsing–remitting MS and secondary progressive MS,[8, 9] the focal lesion load in the spinal cord does not differ significantly among these forms.[9] Thus, a higher proportion of the total MRI lesion load is in the spinal cord in primary progressive MS.[9] However, it should be noted that the lesion load in the spinal cord compared to the brain is low in all forms of MS and therefore might not be as sensitive in detecting differences among the different forms. Some patients with primary progressive MS have spinal cord involvement but minimal or no brain lesions on MRI.[46] Longitudinal MRI studies have shown that new lesions accumulate in the spinal cord at the same rate in primary and secondary progressive MS although the rate of new lesion development in the brain is much lower in primary than in secondary progressive MS.[47] Diffuse MRI abnormalities are more common in the spinal cord, as they are in the brain, in primary progressive MS compared to relapsing–remitting MS and secondary progressive MS.[39] Spinal cord atrophy, determined by measuring spinal cord cross-sectional area on T1-weighted imaging, occurs in primary progressive MS, as in the other forms of MS.[9] The cross-sectional area at the C2 level has a strong inverse correlation with disability measured by Kurtzke's Expanded Disability Status Scale when all MS patients are grouped together,[48] but not within the primary progressive group.[39]

Treatment Of Primary Progressive Ms

Currently there is no effective treatment for primary progressive MS. Interferon β-1b and interferon β-1a make primary progressive MS worse, as manifested by increased spasticity [49] and an increased rate of ventricular enlargement,[50] possibly by inhibiting B-lymphocyte apoptosis and increasing antibody-mediated CNS damage.[51] The development of effective therapy for primary progressive MS will be dependent on a better understanding of the pathogenesis. It has been proposed that depletion of B cells by rituximab may be beneficial in MS and other chronic autoimmune diseases.[16] Such B-cell depletion might be effective by preventing antigen presentation to T cells in the CNS and by preventing autoantibody production.

Acknowledgements

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