Multiple Sclerosis: Autoimmune Disease or Autoimmune Reaction?

Peter K. Stys

ABSTRACT: Multiple sclerosis (MS) is traditionally considered an autoimmune inflammatory demyelinating disease of the central nervous system (CNS) with much knowledge available to support this view. However, this characterization implies that the primary event is an aberrant immune response directed at CNS antigens, promoting inflammation and later driving progressive axo-glial degeneration. Trials with potent anti-inflammatory agents and detailed neuropathological studies raise questions about this sequence of events. This hypothetical paper argues that MS may be primarily a "cytodegenerative" disease, possibly first involving the oligodendrocyte/myelin unit. Liberation of autoantigens secondarily recruits an immune response, the force of which heavily depends on the host's immune predisposition. Thus, the spectrum of MS from highly aggressive Marburg type, to primary progressive disease with little inflammatory burden, is governed by a "convolution" between the underlying cytodegeneration and the host's immune predilection. Clinical heterogeneity may be a reflection of a variable immune response, whereas in reality, the "real MS" may be a homogeneous degenerative process analogous to well known primary neurodegenerative diseases.

RÉSUMÉ: La sclérose en plaques, une maladie auto-immune ou une réaction auto-immune? La sclérose en plaques (SP) est considérée traditionnellement comme une maladie démyélinisante inflammatoire auto-immune du système nerveux central (SNC), une notion bien étayée par de vastes connaissances. Cependant, cette interprétation implique que l'événement primaire est une réponse immunitaire aberrante dirigée contre des antigènes du SNC, qui favorise l'inflammation et subséquemment la dégénérescence axo-gliale progressive. Des essais au moyen d'agents anti-inflammatoires puissants et des études neuropathologiques détaillées soulèvent des questions au sujet de cette succession d'événements. Dans cet article, nous émettons l'hypothèse que la SP puisse être principalement une maladie "cytodégénérative", impliquant possiblement au départ l'unité oligodendrocyte/myéline. La libération d'auto-antigènes recruterait secondairement une réponse immunitaire dont la force dépendrait principalement de la prédisposition immunitaire de l'hôte. Ainsi, le spectre de la SP, de la forme très agressive de Marburg à la forme progressive primaire dont le fardeau inflammatoire est minime, serait régi par une "convolution" entre la cytodégénérescence sous-jacente et la prédisposition immunitaire de l'hôte. L'hétérogénéité clinique pourrait être le reflet d'une réponse immunitaire variable, alors qu'en réalité, la "vraie SP" pourrait être un processus dégénératif homogène analogue à celui des maladies neurodégénératives primaires bien connues.

Can. J. Neurol. Sci. 2010; 37: Suppl. 2 - S16-S23

Multiple sclerosis (MS) is traditionally considered to be a prototypical autoimmune inflammatory disease of the central nervous system, with a primary immune assault aimed at central myelin and the oligodendrocyte[1-6]. In recent years, in addition to the well described inflammatory demyelinating pathology observed in this disease, progressive axonal degeneration has come to attention as an additional important component that leads to permanent and progressive clinical disability[7-9]. Moreover, at least in the early phases, inflammation plays a prominent role and contributes to tissue destruction. While the histopathological changes in the brain and spinal cord white matter of MS patients have been described for over a century[10,11], more recently it is becoming apparent that gray matter structures, both cortical and deep, are involved as well[12-15]. After decades of investigation, unfortunately neither the trigger for the immune response, nor the pathophysiology of axonal degeneration, are known with certainty. Hope for the identification of a single, straightforward cause of this disease is further dimmed by a large body of work pointing to a diverse and multifactorial

From the Department of Clinical Neurosciences, Hotchkiss Brain Institute, University of Calgary, Calgary, Alberta, Canada.

Received April 19, 2010. Final Revisions Submitted April 29, 2010.

Correspondence to: Peter Stys, Department of Clinical Neurosciences, HRIC 1AA22, 3330 Hospital Drive NW, Calgary, Alberta, T2N 4N1, Canada.
E-mail: pstys@ucalgary.ca

etiology. A number of factors have been proposed that predispose individuals to the disease: these include viral etiologies such as Epstein-Barr and human herpes-6 viruses; nutritional deficiencies e.g. vitamin D; significant genetic/hereditary factors; and environmental influences, including sunlight exposure, and a curious but undeniable latitudinal variation, seemingly imprinted at an early age[16-22].

Probably the most compelling observation on the influence of genetics comes from monozygotic twin studies, where a 30% concordance has been consistently observed, dropping off rapidly as the degree of "genetic relatedness" diminishes[22,23]. But the same incomplete degree of concordance in genetically identical individuals also argues in favor of environmental factors, further supported by migrational studies from low-to-high as well as high-to-low risk geographical locations[17]. Last, but certainly not least, is of course the commonly accepted hypothesis of an autoimmune disease directed against an unknown antigen(s) in the central nervous system (CNS), accompanied by relapsing and/or chronic inflammation[5,24]. Clearly, the underlying cause of MS is likely complex and multifactorial, and so after decades of intensive investigation we are unfortunately no closer to understanding the fundamental etiology of this disease. In this article, I will argue in favor of an alternate hypothesis summarized in the Figure, which has been gaining traction in recent years[25-29] for which there is accumulating experimental data. I will further argue how the prominent inflammatory/autoimmune clinical phenotype may have misled us to pursue avenues that have not shed much light on the fundamental underlying cause of MS.

Countless MS-related papers, review articles and book chapters begin with a statement such as "MS is an inflammatory demyelinating disease of the CNS". This has always been, and will always be, correct. The most striking phenotype truly is a situation of brisk inflammation in acute plaques, transient inflammatory lesions on magnetic resonance imaging (MRI) that respond to anti-inflammatory therapies, oligoclonal IgG in the cerebrospinal fluid (CSF) of most patients suggesting at least an inflammatory condition, if not a frank autoimmune disorder, and association with specific HLA types[18]. For all these reasons, testing the hypothesis that "MS is an autoimmune inflammatory demyelinating CNS disease" was very reasonable, and has yielded a wealth of information, which in turn has spurred development of useful medications (understandably, and pursuant to the main hypothesis, all immunomodulatory as their main mechanisms of action). Yet data have begun to appear that challenge this hypothesis. Recent pathological studies on very early lesions from MS patients reveal early loss of oligodendrocytes and myelin (but with minimal or no axonopathy) at borders of active MS lesions. Conspicuously absent are significant numbers of T or B cells, with only scavenging macrophages seen clearing myelin debris; indeed in two very early cases no microglial activation was evident bordering several large plaques[30]. In an ultrastructural examination of biopsy material from MS patients, myelin degeneration in areas beyond foci of maximal inflammation or macrophage infiltration was observed[31]. Moreover, these investigators also noted frequent widening of the inner myelin lamellae in otherwise still-myelinated axons, together with intact axon cylinders and outer myelin wraps. If an extrinsic factor (such as T cells) was primarily responsible for the demyelination, one would expect the oligodendrocyte and outer myelin sheath to be affected first. Taken together, observations such as these are consistent with a scenario whereby the oligodendrocyte/myelin sheath are damaged first by an unknown mechanism, with an immune/inflammatory response arising as a secondary reaction to some primary injury. Given the many factors secreted in inflammatory foci, such as cytokines, glutamate and nitric oxide[1,32-34], such secondary inflammation would add fuel to the simmering fire of the primary insult, further exacerbating parenchymal injury and clinical deficits. Indeed, given that axons are dependent on an intimate relationship with their myelinating oligodendrocyte for long term survival[35], frequent and vigorous inflammatory attacks may finally overwhelm the brain's ability to remyelinate demyelinated lesions[36,37] and bias permanently denuded axons towards irreversible degeneration. Thus, investigators have concluded that a more aggressive inflammatory history early in the disease may condition axons to later degeneration[38,39]. Such a conclusion is plausible and likely correct, however, it does not prove that inflammation was the pivotal event, only an important additional insult that may more strongly drive a non-inflammatory degenerative process that was already operating (dashed line in the Figure). This would explain both the partial success and partial failure of anti-inflammatory therapies in abrogating later progressive disease.

Myelin proteins and lipids are very immunogenic[1,40,41], therefore it is reasonable to propose that primary and then secondary injuries to myelin-containing structures may trigger a brisk inflammatory response in immunologically susceptible hosts. Indeed, it is conceivable that this inflammatory/immune response is so prominent in MS, that it has driven a certain direction of study for decades, perhaps overshadowing alternate hypotheses. Based on the above arguments, we need to consider such an alternate hypothesis, and to examine the consistency of available data with such a conjecture:

> "MS is primarily a cytodegenerative disease, where autoimmunity / inflammation are prominent secondary reactions in predisposed hosts".

This hypothesis, illustrated in the Figure, carries with it a number of implications. First, it suggests that at its core, MS is a slowly progressive degenerative disorder, much like Parkinson's or Alzheimer's diseases, but with a crucial difference: the key elements that predominantly (but not exclusively[12]) degenerate are in the white matter and include myelin, whose constituents are notably encephalitogenic[40]. Second, the host must be immunologically primed to react adversely to degraded or chemically modified autoantigenic white matter components (eg. citrullinated myelin basic protein[42], lipids[43]). After all, many common CNS parenchymal injuries involving white matter such as stroke, brain trauma, spinal cord injuries and dysmyelinating disorders (but see below) cause significant destruction of white matter elements, including myelin, without inducing an MS-like disease. Third, while the oligodendrocyte/myelin unit are the preferred suspects[44], because we do not know which element is the main target of this proposed degenerative process, I will remain noncommittal and retain the generic moniker of a "cytodegeneration"; the axon or even astrocyte may be additional, or even primary, subjects of degeneration. Finally,

https://doi.org/10.1017/S0317167100022393 Published online by Cambridge University Press

and most importantly, if this hypothesis is correct, it would imply that "real MS" is primary progressive disease, leading to the following hypothetical model:

1. MS is a progressive degenerative disease of myelinating glia (and secondarily of axons), and not a relapsing neuroinflammatory disorder. The disease begins subclinically, years before the first overt manifestation, as the CNS attempts to adapt and repair.
2. At a mean age of onset of around 40 years, a progressive disorder is manifest with equal preponderance in males and females[45], which we define as PPMS. Inflammation does not play a significant role in this phase as suggested by the failure of anti-inflammatory therapies to alter progression[29,46].
3. In a certain proportion of patients (as it turns out the vast majority), an aberrant innate and adaptive immune response is raised against autoantigens liberated by the cyto-degeneration posited in #1. As a result, what would have remained a subclinical disorder for years to come, now surfaces a decade earlier: the initially silent degenerative process becomes unmasked by a brisk secondary immune/ inflammatory response, which is recurrent but often reversible clinically and radiologically. This we define as RRMS. Here the female preponderance may simply reflect a higher predilection for autoimmune disease in general among women[47,48].
4. Independent of the inappropriate inflammatory attacks in #3, the underlying degenerative process continues at roughly the same rate as it would have in the absence of relapses. After an average of ten years, the immune/inflammatory response "burns out", and the patient enters a secondary progressive phase. The fact that the mean age of onset of PPMS and SPMS are the same, and the rate and character of progression are very similar in both groups[45,49,50], may not be mere coincidence. In other words, once the recurrent inflammatory waves subside, the two types of MS once again become the "same" disease.
5. A significant percentage of patients exhibit a mix of progressive disease and inflammatory relapses[50,51], so fall somewhere in the gray zone between purely relapsing/ completely remitting versus steadily progressive disease. This is merely a reflection of the wide spectrum of aggression of the underlying immune response, and not because the underlying degenerative process is sometimes oscillatory and other times progressive. Having said this, PPMS itself may exhibit a variable course[52], as is commonly observed in many other primary neurodegenerative disorders.
6. Given that inflammatory CNS lesions produce significant amounts of cytotoxic agents, it stands to reason that such attacks may leave in their wake an additional burden of irreversible parenchymal injury, over and above what is accruing from the underlying degeneration. However, overall the number of early relapses does not seem to significantly influence the course of later progressive disease[39,51], suggesting that the early inflammatory phase may not induce excessive irreversible damage, compared to what lies ahead in the progressive phase.

This model implies that the progressive cytodegenerative white matter disorder, which may be the "real MS", is *convolved* with an aberrant, and highly variable, immune response. In subjects with a sedate immune predilection (the minority) this convolution is weak, and the disease assumes a primary progressive phenotype[45] analogous to other primary neurodegenerative disorders. At the other end of the spectrum, when the immune system is very aggressively primed (also the minority of MS patients), the convolution is very strong, with the result being tumefactive "Marburg type" MS[53,54]. The clinical course in such malignant MS may be fulminant, mirroring the aggressive inflammatory reaction rather than a more rapid underlying degeneration. This is supported by the observation that many of these patients respond to aggressive immuno-supppression early in the course[53,55]. Interestingly, despite an aggressive initial presentation in Marburg MS, later clinical course and progression are not noticeably different from a more typical MS cohort[54]. This may imply that the inflamed brain is remarkably resilient, and equally importantly, that the underlying degenerative mechanisms proceed independently, and are little altered by even aggressive inflammatory attacks. The above illustrates the two extremes of the MS spectrum, with the majority of MS patients falling somewhere in the middle, all determined, at least during the initial phases of their disease, by their immune predilection.

I would argue that the immunological convolution alluded to above is so common, and exerts such a profound effect on the clinical picture early in the course, that it overwhelms the "true" phenotype of MS, morphing the disease from what would have been a progressive degenerative disorder like so many other neurodegenerative diseases, into the classical "relapsing-remitting inflammatory demyelinating disease of the CNS" which MS is mostly known as. As a corollary, if we now define MS as such an inflammatory relapsing remitting disorder, and focus our investigations on this patient population, clinical and laboratory studies will perforce yield information on this immunological convolution, rather than on the underlying hypothetical degenerative mechanism(s). Another important consequence of this variable convolution across MS patient populations, is the major headache it causes epidemiologists who work hard to identify consistent and predictable patterns and progressions, and consequently for clinical trialists who try to devise reliable low-noise outcome measures. This is perhaps the reason why the underlying etiology of MS has not yielded to decades of intensive research effort, though we have learned a tremendous amount about the immunobiology of the secondary response.

Let us now apply the proposed model to what is currently known about MS, in search of possible inconsistencies that may invalidate this alternate hypothesis. Consider for instance genetic studies, and in particular twin studies alluded to previously, as supportive evidence for a strong genetic component in MS. Because the majority of cases are of the relapsing remitting variety, one could equally argue that the strong genetic influence simply reflects a genetic bias of the aberrant immune system, rather than of the "real" disease itself. Taking the argument further, it would be instructive to see whether primary progressive disease shares such strong genetic influences, if we accept for a moment that PPMS is the "true MS". Unfortunately there are insufficient data to draw conclusions about concordance in primary disease (G. Ebers, personal communication). Hypothetically speaking, if such data should

https://doi.org/10.1017/S0317167100022393 Published online by Cambridge University Press

become available in the future and show a weak or non-existent genetic component, this may indicate that the large current body of knowledge on MS genetics is more reflective of genetics of the immune response, rather than of the underlying disease itself – or alternatively, that RRMS and PPMS are two different diseases altogether, which seems less likely. Outcomes with modern therapeutic agents, pointing to an "inflammation/degeneration mismatch"[29], are even more instructive. The humanized monoclonal antibody alemtuzumab (Campath-1H), a powerful lymphocyte depletor, is remarkably effective at reducing relapses and new MRI lesion formation by >90%[38,56]. This attests to its powerful anti-inflammatory effect. Moreover, this agent resulted in improved clinical scores at two years compared to baseline in the relapsing remitting cohort. Curiously, despite a near-complete elimination of clinical relapses and new MRI lesions, the secondary progressive group continued to accumulate disability and exhibited progressive brain atrophy radiologically. A similar experience was noted with rituximab, which depletes B lymphocytes. This agent significantly reduces relapse rates and Gd-enhancing lesions in RRMS patients[57], but failed to significantly alter the course of primary progressive disease[58]. Using a completely different approach, autologous haematopoietic stem cell transplantation also induces pronounced immunosuppression, yet ongoing demyelination and axonal degeneration seem to progress, even with little lymphocytic infiltrate[59]. One would expect that, if MS was primarily an autoimmune/inflammatory disease, potent suppression of this process should halt inflammatory attacks (which it does) as well as later progression, which it does not, at least not as potently as one would expect if inflammation was the primary driver. One could argue that the pre-existing inflammation itself may have set in motion a relentless process that later becomes resistant to anti-inflammatory intervention. Indeed, in the secondary progressive cohort of patients treated with alemtuzumab, subjects with the greatest inflammatory burden at the time of treatment continued to accumulate disability most rapidly. However one could just as easily argue in favor of the alternate hypothesis: it is conceivable that patients with a more malignant hypothetical "cytodegenerative" course initially, would shed more autoantigens, in turn recruiting a more aggressive immune/inflammatory response detected clinically early on. Suppressing the inflammation with an agent such as alemtuzumab, may leave the underlying degenerative process unchecked, with more rapidly progressive cerebral atrophy and clinical disability. The clinical experience may lead us to conclude that brisk early inflammation sets up the CNS for later degeneration. This is not necessarily wrong, but from the previous arguments the same clinical experience is equally consistent with the alternate hypothesis. Being consistent with a hypothesis provides no proof of course, but so far clinical data in no way refute this alternate view. Finally, recent observations indicate a close association between inflammation and ongoing axo-glial degeneration, even in later progressive disease[60]. This is interpreted as evidence that inflammation may continue to drive degeneration during all phases of MS. However, one could also argue that ongoing primary axo-glial degeneration driven instead by an unknown factor, in turn continues to elicit a secondary inflammatory response by virtue of degeneration of cellular elements. The established close correlation between inflammation and degeneration at all stages of the disease makes disentangling this "which comes first" question extremely difficult, but at the same time critically important.

Case reports of certain hereditary disorders of white matter provide further fascinating insight. Warshawsky and colleagues[61] reported a case of a 49-year-old woman with a ten year history of progressive gait abnormality with upper motor neuron signs, nocturia, dysarthria and sensory abnormalities in the feet. Magnetic resonance imaging showed areas of increased signal intensity in the deep cerebral periventricular white matter, and also in the pons, medulla and cervical cord. Visual evoked potentials were abnormal bilaterally and her CSF was positive for oligoclonal bands. A diagnosis of primary progressive MS was made. Interestingly, she had a son who died at age ten of a leukodystrophy. This prompted genetic investigation which revealed a novel mutation of the proteolipid protein 1 (PLP1) gene, a major protein of CNS myelin. This case is highly instructive as it clearly illustrates how a primary defect of myelin structure can result not only in a progressive leukodystrophy that closely mimics the clinical features of PPMS, but also elicited an autoimmune reaction in the form of CSF oligoclonal bands, which was almost certainly secondary to the dysfunctional myelin. Another case of a 47-year-old woman was summarized by Dooley and Wright[62]. The patient complained of episodic paresthesiae in both feet lasting several days, over four years. Examination revealed sensory and upper motor neuron abnormalities in the legs, with decreased hearing and abnormal brainstem evoked potentials. Her CSF was positive for oligoclonal bands. She was diagnosed with MS until her son developed a rapidly progressive illness and was diagnosed with adrenoleukodystrophy. This inherited disorder of very long chain fatty acid metabolism is well known to exhibit inflammatory demyelinating pathology closely resembling MS[63], with Gd-enhancing white matter lesions on MRI[64] and reduced white matter N-acetyl aspartate levels[65], all features typically observed in MS. Finally, even mitochondrial mutations may be associated with an MS-like picture. Harding's disease is an association between Leber's Herediatry Optic Neuropathy (LHON) and MS (or at least an MS-like disease)[66]. In this disorder, the optic neuropathy of LHON is followed by often typical clinical and radiological features of RRMS. As in the previous examples above, many Harding's disease patients also have elevated CSF IgG and oligoclonal bands, and many (but not all) respond to corticosteroid treatment initially. One interpretation is of a mere chance association of LHON and MS in the occasional unfortunate patient, with the optic neuropathy due to the LHON mitochondrial defect, and the other signs and symptoms due to the MS. This may be correct except that the prevalence rates of LHON and MS indicate that in Harding's these two diseases coexist 50 times more frequently than expected by chance[66]. An equally plausible, and in my opinion a more parsimonious and compelling explanation in the context of the previous examples, is that Harding's is really only one disease of mitochondrial metabolism, preferentially affecting white matter elements, in which some patients are immunologically primed to react to autoantigens liberated by energy-starved and degenerating white matter components[67]; this abnormal immune disposition results in a syndrome closely approximating many features of typical MS. Indeed, the greater penetrance of LHON in males results in

https://doi.org/10.1017/S0317167100022393 Published online by Cambridge University Press

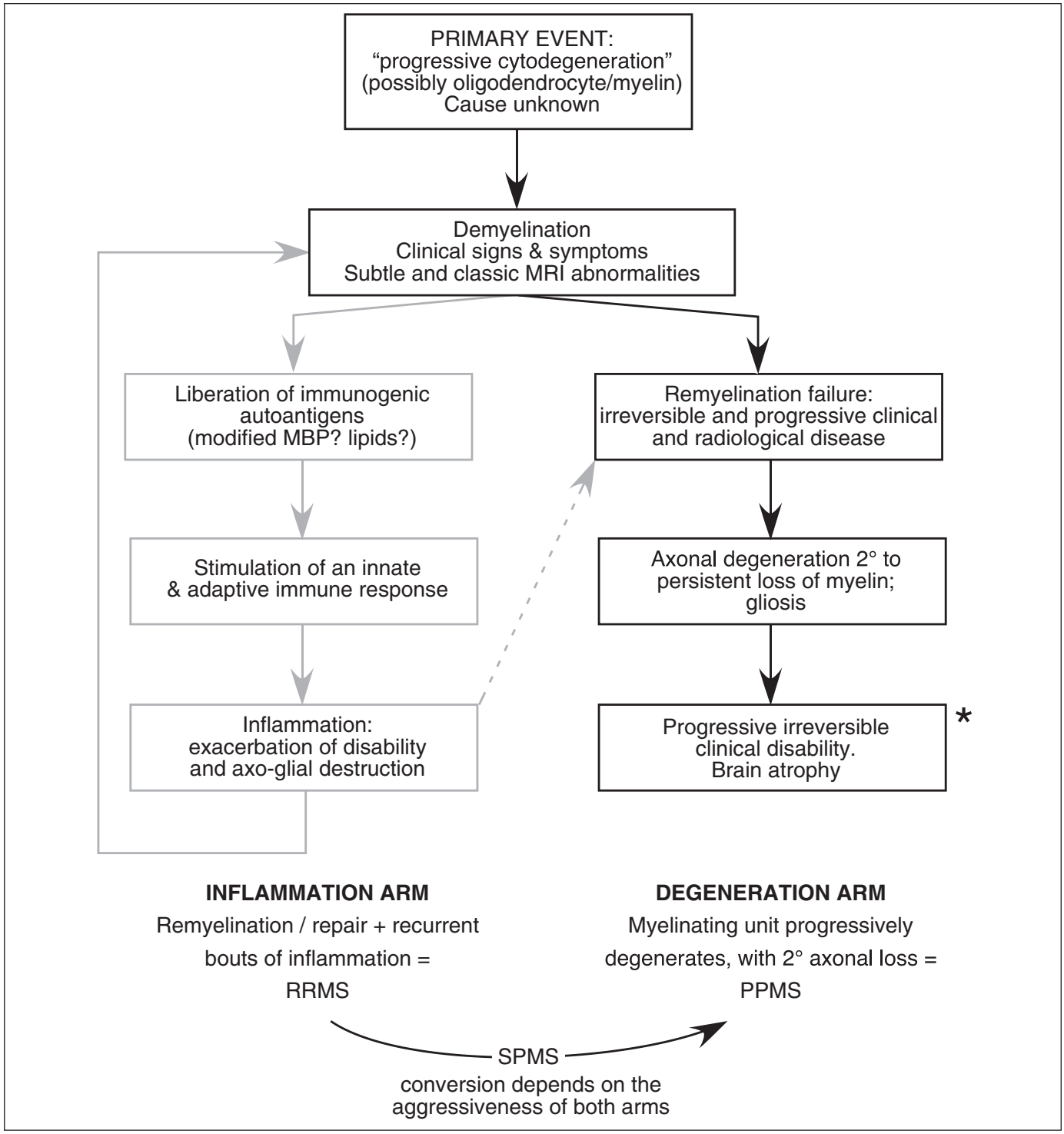

Figure: *Hypothetical model illustrating how MS may be primarily caused by a cytodegenerative process aimed at the oligodendrocyte/myelin complex. Gradual degeneration of these elements will lead to clinical disability and radiological abnormalities due to demyelination of vital CNS pathways. The disease can then follow one of two arms which are not mutually exclusive, and in fact, frequently overlapping. Because of their immune predilection and the immunogenicity of myelin constituents, initially most patients overtly follow the "inflammation arm" on the left (gray boxes), in a cyclic pattern, defined as relapsing-remitting disease. Inflammatory attacks per se promote additional demyelination on top of what the cytodegenerative process may have caused, producing further disability and tissue damage. Some patients exhibit a very weak autoimmune/inflammatory reaction and proceed down the degenerative arm, typical of many other primary neurodegenerative diseases. The persistent demyelination in turn promotes permanent axonal degeneration, brain atrophy and progressive clinical disability. Given enough time, most patients proceed to the box at the lower right (*); it is unclear whether any current treatments significantly alter this ultimate destiny. Pathogenetically speaking, the "real MS" is represented by the black boxes, with the gray boxes representing a reaction to the former, albeit a very important one. In this model, degeneration does not follow inflammation, but precedes then parallels it.*

https://doi.org/10.1017/S0317167100022393 Published online by Cambridge University Press

77% of "plain" LHON cases being male, whereas the majority of Harding's patients (with the same mitochondrial mutation) are female. One can speculate that the reason for this as mentioned earlier, is that females have a greater predisposition to autoimmune disease in general[47], so that when the CNS is challenged and leaks autoantigens, females will have a greater chance of reacting with an autoimmune/inflammatory phenotype versus males who will suffer a progressive non-relapsing, non-inflammatory, more characteristic degenerative course. The parallel between inflammatory RRMS being more common in females versus the less inflammatory and more "degenerative" phenotype of PPMS, where no female preponderance exists, comes to mind. These cases illustrate how clearly defined metabolic defects involving white matter elements (in particular those resulting in demyelination which is the most likely source of relevant autoantigens), may precipitate, in certain predisposed individuals, a disorder exhibiting immune and inflammatory features that are virtually indistinguishable from MS on clinical, radiological and laboratory grounds.

This alternate model (Figure) may explain additional conundrums, for instance, the recurrent association between MS and certain microbes, in particular Epstein-Barr (EB) virus[68,69]. There is strong evidence that prior EB virus infection predisposes individuals to developing MS later in life, yet a mechanism has so far not been discovered. While it is possible that EB virus somehow "causes" MS, it is equally possible that EB virus alters the behavior of a host's lymphocytes so that if a degenerative process targeting the oligodendrocyte/myelin complex arises, this host will be more likely to respond with an inflammatory phenotype. Therefore the association between MS and EB virus may only exist because as defined, "MS" is by far the most commonly inflammatory relapsing remitting disease. Put another way, EB virus may simply strengthen the proposed "immuno-logical convolution" by virtue of its effects on lymphocytes[69], and may have no connection whatsoever with the true cause of MS. Indeed, the association between EB virus and a diverse array of autoimmune diseases ranging from systemic lupus, to rheumatoid arthritis, and autoimmune hepatitis[70-72] would argue in favor of this virus' ability to modulate the immune response against an autoantigen, rather than being directly responsible for causing such a diverse group of disorders. If the above argument is correct, the prediction would be that the association between MS and EB virus would disappear if PPMS was considered instead. Indeed, this concept of strong correlations with MS, if defined as an inflammatory (RRMS) instead of a degenerative (PPMS) disorder, can be applied to many different associations (both genetic and environmental) that have been detected over the decades; in the end many of these conclusions about etiopathogenesis of MS may be misleading, reflecting the genetic or environmental influence on the immune response itself, rather than on the root cause of MS. By corollary, I would argue that to identify potentially important genetic and/or environmental etiologies, we need to redefine MS as PPMS, and extend these studies in this patient population.

Conclusion

Decades of intensive clinical and laboratory investigation have unequivocally established inflammation as a prominent feature of MS that contributes to tissue damage in the CNS, and to transient, and possibly to progressive, clinical disability. The detailed dissection of the complex immunopathogenesis of MS has in turn resulted in a number of medications that have clearly benefitted countless patients, at least in the early phase of the disease where inflammatory phenomena dominate. Therefore, the important role of inflammation and significant (albeit partial) efficacy of agents designed to counteract its effects are beyond dispute. However, these facts should not necessarily be construed as indicators of underlying fundamental disease mechanisms. One can draw an interesting analogy with peptic ulcer disease: it has been accepted for decades that excess stomach acid secretion is linked to gastro-duodenal ulcers, and in response, antacid therapies are highly successful at controlling many of the symptoms and complications. Yet we now know that the underlying cause of this disorder is infection with the *Helicobacter pylori* bacterium, a rather startling conclusion to this story. This serves as an important reminder that what appears obvious may culminate in a very different and unexpected finish. The arguments presented in this paper are by no means meant to minimize the importance of the immune system and inflammation in MS, but rather, to make the point that to date all of our clinical and laboratory experience is equally consistent with the "cytodegeneration first with inflammation/autoimmunity second" hypothesis as the fundamental mechanism of this disease. Indeed, the debate of which comes first in the field of MS has become more heated recently, and perhaps the main challenge for MS research in this coming decade is to unequivocally decipher this fundamentally important chicken versus egg paradox.

Acknowledgements

The author thanks Drs. S. Tsutsui , C. Power and V. W. Yong for helpful discussion. Work in the author's laboratory is supported by the Canadian Institutes for Health Research, Canada Foundation for Innovation, Alberta Heritage Foundation for Medical Research, the Dr. Frank Leblanc Chair for Spinal Cord Research, Canada Research Chairs and an AHFMR Scientist award.

References

1. Bhat R, Steinman L. Innate and adaptive autoimmunity directed to the central nervous system. Neuron. 2009; 64: 123-32.
2. Prat A, Antel J. Pathogenesis of multiple sclerosis. Curr Opin Neurol. 2005; 18: 225-30.
3. Agrawal SM, Yong VW. Immunopathogenesis of multiple sclerosis. Int Rev Neurobiol. 2007; 79: 99-126.
4. Frohman EM, Racke MK, Raine CS. Multiple sclerosis--the plaque and its pathogenesis. N Engl J Med. 2006; 354: 942-55.
5. Compston A, Coles A. Multiple sclerosis. Lancet. 2008; 372: 1502-17.
6. Waxman SG. Axonal conduction and injury in multiple sclerosis: the role of sodium channels. Nat Rev Neurosci. 2006; 7: 932-41.
7. Trapp BD, Peterson J, Ransohoff RM, Rudick R, Mork S, Bo L. Axonal transection in the lesions of multiple sclerosis. N Engl J Med. 1998; 338: 278-85.
8. Trapp BD, Stys PK. Virtual hypoxia and chronic necrosis of demyelinated axons in multiple sclerosis. Lancet Neurol. 2009; 8: 280-91.
9. Frohman EM, Filippi M, Stuve O, et al. Characterizing the mechanisms of progression in multiple sclerosis: evidence and new hypotheses for future directions. Arch Neurol. 2005; 62: 1345-56.

10. Kornek B, Lassmann H. Axonal pathology in multiple sclerosis. A historical note. Brain Pathol. 1999; 9: 651-6.
11. Lassmann H. The pathology of multiple sclerosis and its evolution. Philos Trans R Soc Lond B Biol Sci. 1999; 354: 1635-40.
12. Geurts JJ, Stys PK, Minagar A, Amor S, Zivadinov R. Gray matter pathology in (chronic) MS: Modern views on an early observation. J Neurol Sci. 2009;
13. Vercellino M, Masera S, Lorenzatti M, et al. Demyelination, inflammation, and neurodegeneration in multiple sclerosis deep gray matter. J Neuropathol Exp Neurol. 2009; 68: 489-502.
14. Rudick RA, Trapp BD. Gray-matter injury in multiple sclerosis. N Engl J Med. 2009; 361: 1505-6.
15. Bo L. The histopathology of grey matter demyelination in multiple sclerosis. Acta Neurol Scand Suppl. 2009; 51-7.
16. Giraudon P, Bernard A. Chronic viral infections of the central nervous system: Aspects specific to multiple sclerosis. Rev Neurol (Paris). 2009; 165: 789-95.
17. Kurtzke JF. Epidemiology and etiology of multiple sclerosis. Phys Med Rehabil Clin N Am. 2005; 16: 327-49.
18. Kantarci O, Wingerchuk D. Epidemiology and natural history of multiple sclerosis: new insights. Curr Opin Neurol. 2006; 19: 248-54.
19. Ascherio A, Munger KL. Environmental risk factors for multiple sclerosis. Part II: Noninfectious factors. Ann Neurol. 2007; 61: 504-13.
20. Pugliatti M, Harbo HF, Holmoy T, et al. Environmental risk factors in multiple sclerosis. Acta Neurol Scand Suppl. 2008; 188: 34-40.
21. Oksenberg JR, Baranzini SE, Sawcer S, Hauser SL. The genetics of multiple sclerosis: SNPs to pathways to pathogenesis. Nat Rev Genet. 2008; 9: 516-26.
22. Ebers GC. Environmental factors and multiple sclerosis. Lancet Neurol. 2008; 7: 268-77.
23. Hawkes CH, Macgregor AJ. Twin studies and the heritability of MS: a conclusion. Mult Scler. 2009; 15: 661-7.
24. Lassmann H. Models of multiple sclerosis: new insights into pathophysiology and repair. Curr Opin Neurol. 2008; 21: 242-7.
25. Huizinga R, Linington C, Amor S. Resistance is futile: antineuronal autoimmunity in multiple sclerosis. Trends Immunol. 2008; 29: 54-60.
26. Bruck W. Inflammatory demyelination is not central to the pathogenesis of multiple sclerosis. J Neurol. 2005; 252 Suppl 5: 10-15.
27. Trapp BD, Nave KA. Multiple sclerosis: an immune or neurodegenerative disorder? Annu Rev Neurosci. 2008; 31:247-69.
28. Confavreux C, Vukusic S. Accumulation of irreversible disability in multiple sclerosis: from epidemiology to treatment. Clin Neurol Neurosurg. 2006; 108: 327-32.
29. Charil A, Filippi M. Inflammatory demyelination and neurodegeneration in early multiple sclerosis. J Neurol Sci. 2007; 259: 7-15.
30. Henderson AP, Barnett MH, Parratt JD, Prineas JW. Multiple sclerosis: distribution of inflammatory cells in newly forming lesions. Ann Neurol. 2009; 66: 739-53.
31. Rodriguez M, Scheithauer B. Ultrastructure of multiple sclerosis. Ultrastruct Pathol. 1994; 18: 3-13.
32. Barger SW, Basile AS. Activation of microglia by secreted amyloid precursor protein evokes release of glutamate by cystine exchange and attenuates synaptic function. J Neurochem. 2001; 76: 846-54.
33. Smith KJ, Lassmann H. The role of nitric oxide in multiple sclerosis. Lancet Neurol. 2002; 1: 232-41.
34. Hohlfeld R. Biotechnological agents for the immunotherapy of multiple sclerosis. Principles, problems and perspectives. Brain. 1997; 120: 865-916.
35. Nave KA, Trapp BD. Axon-glial signaling and the glial support of axon function. Annu Rev Neurosci. 2008; 31: 535-61.
36. Patrikios P, Stadelmann C, Kutzelnigg A, et al. Remyelination is extensive in a subset of multiple sclerosis patients. Brain. 2006; 129: 3165-72.
37. Goldschmidt T, Antel J, Konig FB, Bruck W, Kuhlmann T. Remyelination capacity of the MS brain decreases with disease chronicity. Neurology. 2009; 72: 1914-21.
38. Coles AJ, Wing MG, Molyneux P, et al. Monoclonal antibody treatment exposes three mechanisms underlying the clinical course of multiple sclerosis. Ann Neurol. 1999; 46: 296-304.
39. Scalfari A, Neuhaus A, Degenhardt A, et al. The natural history of multiple sclerosis, a geographically based study 10: relapses and long-term disability. Brain. 2010 Jul;133(Pt 7):1914-29.
40. Bielekova B, Goodwin B, Richert N, et al. Encephalitogenic potential of the myelin basic protein peptide (amino acids 83-99) in multiple sclerosis: results of a phase II clinical trial with an altered peptide ligand. Nat Med. 2000; 6: 1167-75.
41. Podbielska M, Hogan EL. Molecular and immunogenic features of myelin lipids: incitants or modulators of multiple sclerosis? Mult Scler. 2009; 15: 1011-29.
42. Moscarello MA, Mastronardi FG, Wood DD. The role of citrullinated proteins suggests a novel mechanism in the pathogenesis of multiple sclerosis. Neurochem Res. 2007; 32: 251-6.
43. Kanter JL, Narayana S, Ho PP, et al. Lipid microarrays identify key mediators of autoimmune brain inflammation. Nat Med. 2006; 12: 138-43.
44. Antel J. Oligodendrocyte/myelin injury and repair as a function of the central nervous system environment. Clin Neurol Neurosurg. 2006; 108: 245-9.
45. Miller DH, Leary SM. Primary-progressive multiple sclerosis. Lancet Neurol. 2007; 6: 903-12.
46. Rojas JI, Romano M, Ciapponi A, Patrucco L, Cristiano E. Interferon beta for primary progressive multiple sclerosis. Cochrane Database Syst Rev. 2009; CD006643.
47. Cooper GS, Stroehla BC. The epidemiology of autoimmune diseases. Autoimmun Rev. 2003; 2: 119-25.
48. Dyment DA, Ebers GC, Sadovnick AD. Genetics of multiple sclerosis. Lancet Neurol. 2004; 3: 104-10.
49. Kremenchutzky M, Rice GP, Baskerville J, Wingerchuk DM, Ebers GC. The natural history of multiple sclerosis: a geographically based study 9: observations on the progressive phase of the disease. Brain. 2006; 129: 584-94.
50. Confavreux C, Vukusic S. Natural history of multiple sclerosis: a unifying concept. Brain. 2006; 129: 606-16.
51. Confavreux C, Vukusic S, Moreau T, Adeleine P. Relapses and progression of disability in multiple sclerosis. N Engl J Med. 2000; 343: 1430-8.
52. Cottrell DA, Kremenchutzky M, Rice GP, et al. The natural history of multiple sclerosis: a geographically based study. 5. The clinical features and natural history of primary progressive multiple sclerosis. Brain. 1999; 122: 625-39.
53. Capello E, Mancardi GL. Marburg type and Balo's concentric sclerosis: rare and acute variants of multiple sclerosis. Neurol Sci. 2004; 25 Suppl 4: S361-3.
54. Lucchinetti CF, Gavrilova RH, Metz I, et al. Clinical and radiographic spectrum of pathologically confirmed tumefactive multiple sclerosis. Brain. 2008; 131: 1759-75.
55. Capello E, Vuolo L, Gualandi F, et al. Autologous haematopoietic stem-cell transplantation in multiple sclerosis: benefits and risks. Neurol Sci. 2009; 30 Suppl 2: S175-7.
56. Jones JL, Coles AJ. Spotlight on alemtuzumab. Int MS J. 2009 Sep; 16(3):77-81.
57. Hauser SL, Waubant E, Arnold DL, et al. B-cell depletion with rituximab in relapsing-remitting multiple sclerosis. N Engl J Med. 2008; 358: 676-88.
58. Hawker K, O'Connor P, Freedman MS, et al. Rituximab in patients with primary progressive multiple sclerosis: results of a randomized double-blind placebo-controlled multicenter trial. Ann Neurol. 2009; 66: 460-71.
59. Metz I, Lucchinetti CF, Openshaw H, et al. Autologous haematopoietic stem cell transplantation fails to stop demyelination and neurodegeneration in multiple sclerosis. Brain. 2007; 130: 1254-62.
60. Frischer JM, Bramow S, Dal-Bianco A, et al. The relation between inflammation and neurodegeneration in multiple sclerosis brains. Brain. 2009; 132: 1175-89.
61. Warshawsky I, Rudick RA, Staugaitis SM, Natowicz MR. Primary progressive multiple sclerosis as a phenotype of a PLP1 gene mutation. Ann Neurol. 2005; 58: 470-3.

62. Dooley JM, Wright BA. Adrenoleukodystrophy mimicking multiple sclerosis. Can J Neurol Sci. 1985; 12: 73-4.
63. Moser HW. Adrenoleukodystrophy: phenotype, genetics, pathogenesis and therapy. Brain. 1997; 120: 1485-508.
64. Kumar AJ, Rosenbaum AE, Naidu S, et al. Adrenoleukodystrophy: correlating MR imaging with CT. Radiology. 1987; 165: 497-504.
65. Kruse B, Barker PB, van Zijl PC, Duyn JH, Moonen CT, Moser HW. Multislice proton magnetic resonance spectroscopic imaging in X-linked adrenoleukodystrophy. Ann Neurol. 1994; 36: 595-608.
66. Palace J. Multiple sclerosis associated with Leber's Hereditary Optic Neuropathy. J Neurol Sci. 2009; 286: 24-7.
67. Kovacs GG, Hoftberger R, Majtenyi K, et al. Neuropathology of white matter disease in Leber's hereditary optic neuropathy. Brain. 2005; 128: 35-41.
68. Salvetti M, Giovannoni G, Aloisi F. Epstein-Barr virus and multiple sclerosis. Curr Opin Neurol. 2009; 22: 201-6.
69. Lunemann JD, Kamradt T, Martin R, Munz C. Epstein-barr virus: environmental trigger of multiple sclerosis? J Virol. 2007; 81: 6777-84.
70. Vaughan JH. The Epstein-Barr virus in autoimmunity. Springer Semin Immunopathol. 1995; 17: 203-30.
71. Poole BD, Scofield RH, Harley JB, James JA. Epstein-Barr virus and molecular mimicry in systemic lupus erythematosus. Autoimmunity. 2006; 39: 63-70.
72. Vento S, Guella L, Mirandola F, et al. Epstein-Barr virus as a trigger for autoimmune hepatitis in susceptible individuals. Lancet. 1995; 346: 608-9.

https://doi.org/10.1017/S0317167100022393 Published online by Cambridge University Press