REVIEW ARTICLE

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Multiple Sclerosis

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MULTIPLE SCLEROSIS IS THE MOST PREVALENT CHRONIC INFLAMMATORY disease of the central nervous system (CNS), affecting more than 2 million people worldwide (at least 400,000 in the United States),[1] and it is currently incurable. It is punctuated by fully or partially reversible episodes of neurologic disability, usually lasting days or weeks. Typical syndromes at presentation include, but are not limited to, monocular visual loss due to optic neuritis, limb weakness or sensory loss due to transverse myelitis, double vision due to brain-stem dysfunction, or ataxia due to a cerebellar lesion.[2] After typically 10 to 20 years, a progressive clinical course develops in many of the persons affected, eventually leading to impaired mobility and cognition; approximately 15% of patients have a progressive course from onset. More than a dozen disease-modifying medications are available to reduce the frequency of transient episodes of neurologic disability and limit the accumulation of focal white-matter lesions on magnetic resonance imaging (MRI). No medication fully prevents or reverses the progressive neurologic deterioration, characterized most commonly by impaired ambulation, loss of bladder control, and slowed cognitive processing, but the question of whether disease-modifying medications can delay clinical progression is controversial.[3-5] The annual economic cost of multiple sclerosis in the United States is approximately $10 billion.[6]

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PATHOLOGY

The idea that multiple sclerosis is a disseminated plaque-like sclerosis was established approximately 150 years ago; indeed, the demonstration of dissemination — in space (disease-related changes in multiple regions of the CNS, including white matter, gray matter, brain stem, spinal cord, and optic nerve) (Fig. 1) and time — forms the cornerstone of diagnosis of the disease. Our understanding of the details of that pathology, and especially how it evolves over time, has been revolutionized with modern techniques such as immunohistochemical staining and MRI.

Multiple sclerosis lesions can appear throughout the CNS and are most easily recognized in the white matter as focal areas of demyelination, inflammation, and glial reaction. Evidence from MRI and pathological assessment (biopsies and autopsies) indicates that the earliest stages of white-matter demyelination (known as early active white-matter lesions) are heterogeneous[7] and evolve over the course of months. Regardless of the particular immunologic pattern of early demyelination (Fig. 2), analysis of active lesions, over both time and space, suggests that a single immune-effector mechanism dominates in each person.[8] Consistent with this notion are the observations that plasma exchange, which removes pathogenic antibodies from the circulation, ameliorates relapses that are refractory to initial treatment with glucocorticoids in patients whose active lesions contain immunoglobulin and complement[9] and that cerebrospinal fluid (CSF) profiles differ according to lesion

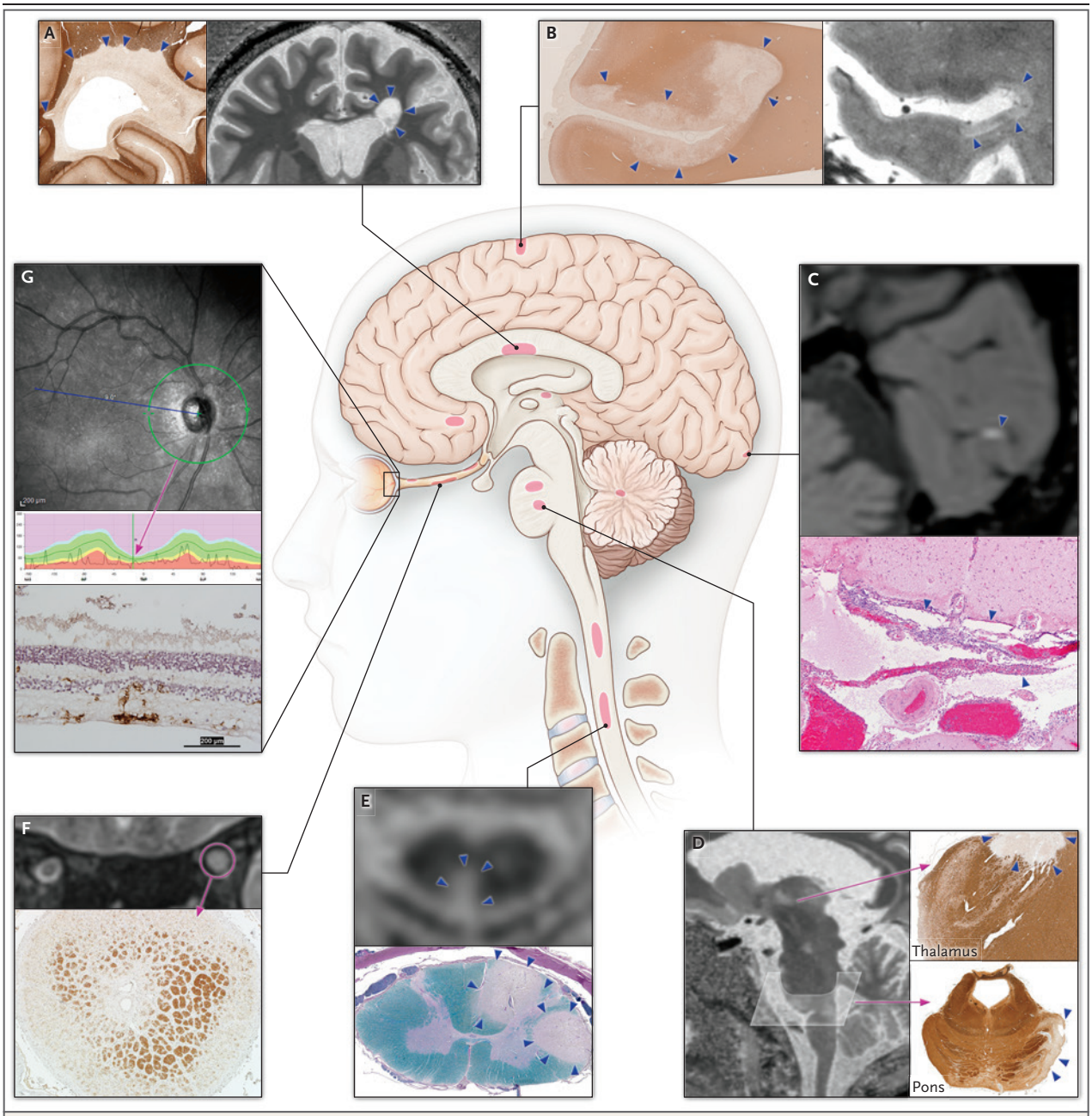

Figure 1. Topography of Multiple Sclerosis Lesions.

Shown is a schematic of lesion location, calling out imaging and pathological examples, in the periventricular white matter (inset A), subpial cortex (B), leptomeninges (C), thalamus and pons (D), spinal cord (E), optic nerve (F), and retina (G). Insets A, B, and D show a 7-tesla MRI of a 40-year-old woman with relapsing–remitting multiple sclerosis, with similar pathological findings (in different patients) highlighted by immunohistochemical staining directed against myelin proteolipid protein. Inset C shows a 3-tesla MRI after the administration of gadolinium in a 35-year-old woman with secondary progressive multiple sclerosis, with corresponding pathological findings in the meninges of a different patient (hematoxylin and eosin staining). Inset E shows a 3-tesla MRI of a 60-year-old woman with relapsing–remitting multiple sclerosis and corresponding pathological findings in a different patient (Luxol fast blue–periodic acid Schiff staining). Inset F shows a 3-tesla MRI of a 31-year-old woman with relapsing–remitting multiple sclerosis and corresponding pathological findings in a different patient (anti–proteolipid protein immunohistochemical staining). Inset G shows a spectral-domain optical coherence tomographic reconstruction illustrating thinning of the peripapillary retinal nerve fiber layer. The normal range of retinal thickness is shown in green, and for this particular patient (black line), the retina is thinner than in 99% of control eyes. The bottom panel of the inset shows corresponding pathological findings in a different patient (immunohistochemical staining for Iba-1, a macrophage and microglial marker, with hematoxylin counterstaining). In all insets, lesions are indicated with arrowheads or circles.

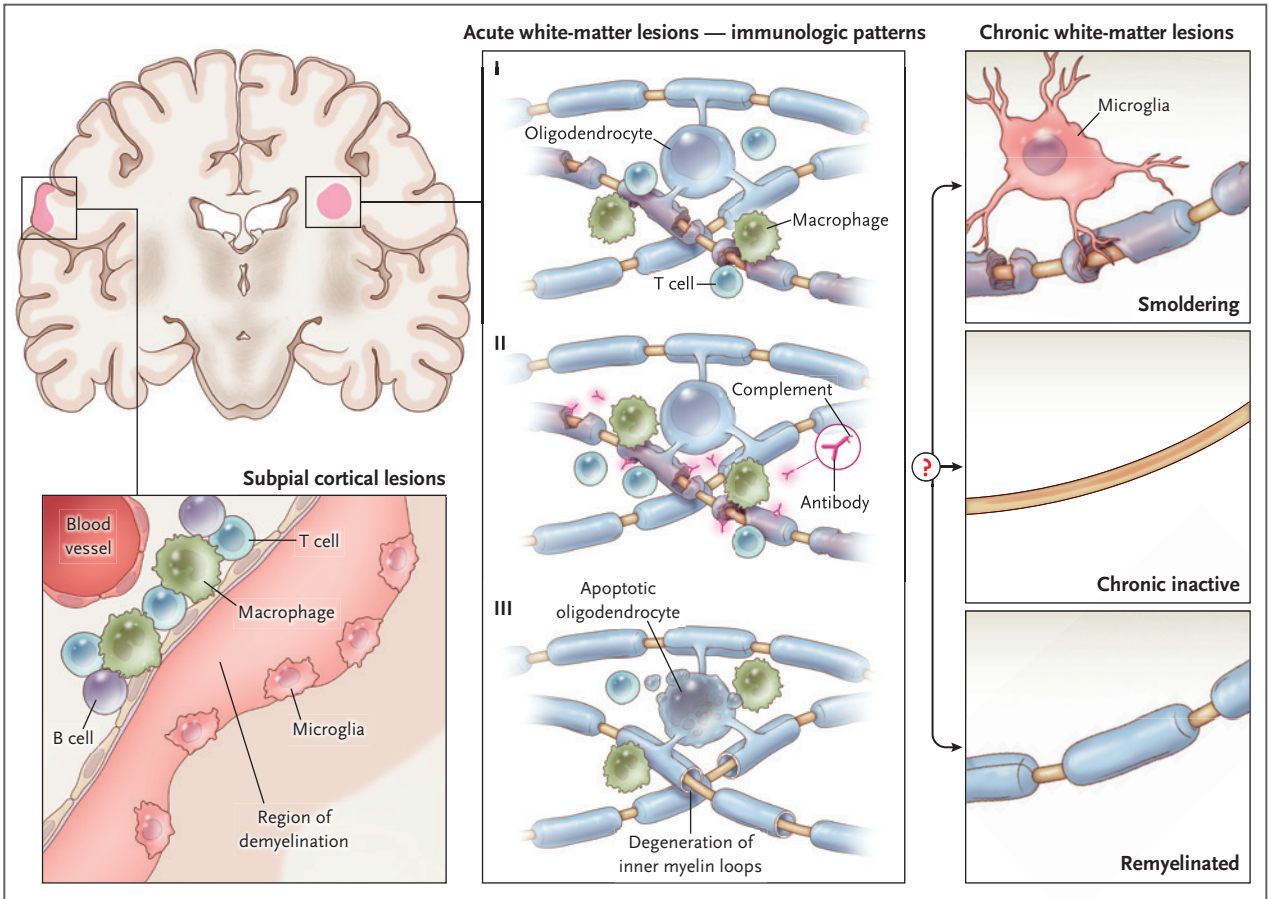

Figure 2. Lesions of the White Matter and Gray Matter.

Early active white-matter demyelination falls into three major categories. The most common types (patterns I and II) show a background of mononuclear phagocytes with perivascular and parenchymal T-cell infiltration. Pattern II is further distinguished by immunoglobulin and complement deposition. In approximately 25% of biopsied active lesions (pattern III), oligodendrocyte apoptosis is accompanied by a "dying-back" oligodendrogliopathy, starting at the portion of myelin closest to the axon. These lesions resemble viral, toxic, and ischemic processes and can be destructive. After the acute phase, factors that remain poorly understood determine whether surviving axons in a lesion are invested by a thin myelin sheath (remyelinated), whether inflammation resolves without remyelination (chronic inactive), or whether inflammation and slow myelin degeneration persist (smoldering). Smoldering lesions are most common in progressive multiple sclerosis. The subpial cortical lesion, which is also more common in progressive multiple sclerosis, is characterized by demyelination of the superficial cortex, possibly in association with inflammation in the overlying leptomeninges and sparse macrophages and microglia at the border between demyelinated and myelinated neuropil.

pattern.[10] The identification of noninvasive biomarkers that correlate with active lesion patterns will facilitate the design of personalized therapeutic strategies for multiple sclerosis, since current treatment algorithms may not adequately address the underlying pathogenic heterogeneity of this complex disease.

What determines the long-term fate of a given lesion — whether the inflammation resolves or "smolders" or whether it remyelinates — is not well understood. Recent data from longitudinal imaging studies suggest that lesions that form in younger people may repair more effectively,[11] a finding consistent with preclinical work indicating that age strongly modulates immune-mediated regenerative processes.[12,13] What remains unclear is whether lesions can remyelinate years after a smoldering lesion is established and whether remyelinated lesions have heightened susceptibility to recurrent demyelination. High-resolution, ultra-high-field (7-tesla) MRI shows promise as a tool for noninvasive staging of lesions,[14] and it will be important for future studies to investigate the relationship between lesion outcomes and clinical status.

Myelin is not exclusive to white matter, and demyelination in multiple sclerosis also involves gray matter.[15-17] Approximately half of cortical lesions are perivascular. In some cortical lesions, the inflamed vessel may be located near the leukocortical junction, in which case demyelination also affects the juxtacortical white matter. Sometimes, a small penetrating cortical vein is involved and only central cortical layers are affected. Cortical lesions are less inflammatory than their white-matter counterparts and have substantially less permeability of the blood–brain barrier.[18]

The remaining cortical lesions do not arise from a single cortical vessel but rather appear to proceed inward from the pial surface of the brain. In autopsies conducted after decades of disease, most such lesions are found to be inactive, in contrast to subpial lesions in early multiple sclerosis, which are inflammatory and topographically associated with diffuse and focal leptomeningeal inflammatory aggregates (especially when observed in biopsy specimens).[17] Subpial lesions can be extensive and are often found on flanking cortical banks within a sulcus, which strongly suggests a leptomeningeal origin. Leptomeningeal inflammation can organize into self-sustaining structures akin to tertiary lymphoid follicles.[19] Although findings on MRI support an association between leptomeningeal inflammation and subpial cortical demyelination,[20] robust detection methods are lacking, and the natural history of such lesions — and their responsiveness to therapy — remain unknown.

Spinal cord lesions are a major source of clinical disability. Perivascular and circumferential demyelination is often highly inflammatory and can involve gray matter.[21] Spinal cord atrophy results from focal inflammatory demyelination and remote neuroaxonal degeneration.[22] It is detectable by MRI, and the cross-sectional area of the spinal cord is therefore a promising outcome measure for clinical trials.[23,24]

As part of the CNS, the optic nerve is also a major target in multiple sclerosis, and loss of the contiguous retinal ganglion cells is well documented.[25] Retinal damage can be assessed in vivo by means of optical coherence tomography,[26] which reveals substantial thinning of the retinal nerve-fiber and ganglion-cell layers despite their lack of myelin. Thinning results from injury to axons in the optic nerve, which are derived from retinal ganglion cells and which succumb to a dying-back process after retrobulbar inflammatory demyelination in acute optic neuritis. Studies have clearly shown concomitant retinal ganglion-cell loss[27] even in the absence of clinical optic neuritis, presumably reflecting either subclinical inflammation of the optic nerve or retrograde transsynaptic degeneration.

EPIDEMIOLOGY

It is not known whether multiple sclerosis has a single or multiple causes, and rarely (if ever) has a specific etiologic trigger been identified. Nonetheless, various genetic and environmental risk factors have been found (Fig. 3).[28] For unknown reasons, approximately three quarters of people with multiple sclerosis are women, as is common in diseases that are considered autoimmune. People with an affected first-degree relative have a 2 to 4% risk of multiple sclerosis (as compared with approximately 0.1% risk in the general population), and concordance in monozygotic twins is 30 to 50%. Genomewide association studies, based on samples assembled from thousands of patients with multiple sclerosis and matched controls, have identified more than 200 gene variants that raise the risk of the disease, of which the most significant remains the HLA DRB1*1501 haplotype (with an odds ratio of approximately 3). Most risk alleles are associated with immune-pathway genes, a finding consistent with the notion that autoimmune mechanisms are paramount in the development of clinical multiple sclerosis. We are currently unaware of any validated genetic risk factor that strongly influences the clinical course of the disease; this limitation reflects the difficulty of measuring disease severity in a disease that evolves over a period of decades.

Major environmental risk factors include geographic latitude (with a higher incidence in more temperate climates), which may reflect seasonal changes in sunlight exposure influencing vitamin D levels or pathogens prevalent in these regions, although a genetic contribution is possible as well. Tobacco exposure, obesity, and mononucleosis are also associated with an enhanced risk of multiple sclerosis. Mononucleosis results from infection with Epstein–Barr virus in the postpubertal population, and multiple sclerosis eventually develops in only a minority of

people with a history of mononucleosis (and a tiny minority of all those infected with the nearly ubiquitous Epstein–Barr virus). Viruses other than Epstein–Barr virus have been suggested as potential causes of multiple sclerosis or of multiple sclerosis–related disease activity, but none have been definitively proved. Some of these viruses may act as molecular mimics, whereas others may interfere with mechanisms that normally limit self-reactive cells. Differential susceptibility is reflected in the mouse model of multiple sclerosis, experimental autoimmune encephalomyelitis (EAE), such that specific myelin antigens are required to induce EAE in different strains of mice.[29] Along these lines, an interesting set of experiments showed that components of the intestinal microbiome can also strongly influence the propensity for the development of EAE, especially in genetically predisposed mouse strains with transgenes for myelin recognition by B cells and T cells,[30] and evidence for a similar phenomenon in patients with multiple sclerosis is beginning to emerge.[31,32] Overall, the mechanisms by which genetic polymorphisms and environmental exposures raise the risk of multiple sclerosis remain the subject of intense investigation.

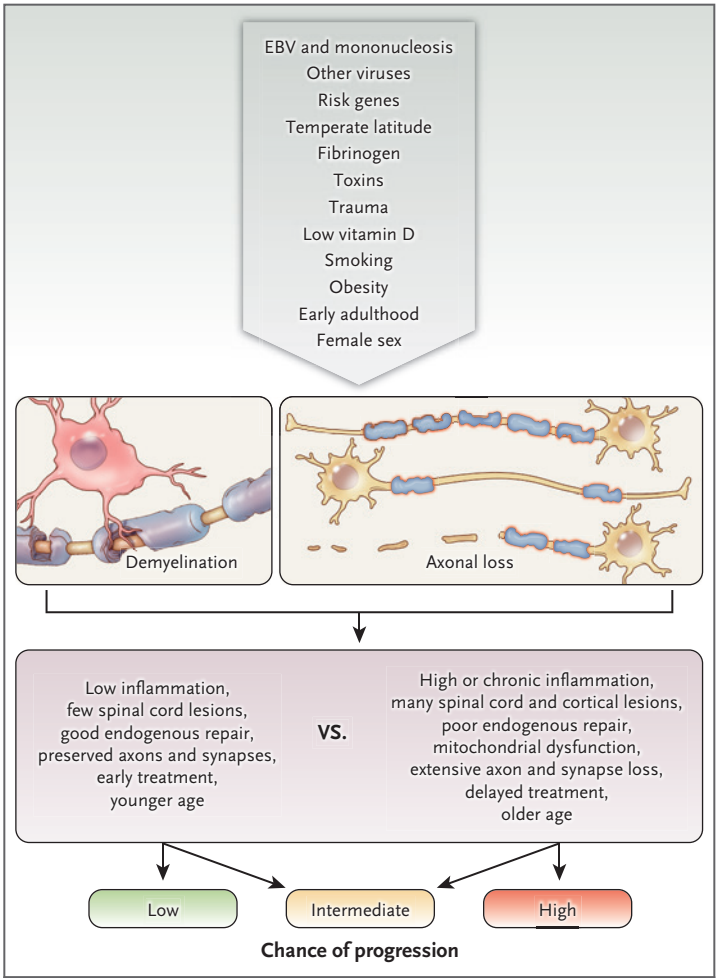

Figure 3. Risk Factors, Triggers, Modifiers, and Disease Courses.
It is unlikely that multiple sclerosis will ultimately be attributed to a single cause. Rather, the genetic and environmental factor or combination of factors that result in a predisposition to multiple sclerosis, initiate the disease, and modify its course are highly diverse from one person to the next. The top portion of the figure shows the funneling of proposed factors, for which varying levels of evidence exist, into the development of inflammatory, demyelinating lesions with heterogeneous axonal loss (middle portion). The bottom portion of the figure lists features of the lesions and their consequences that are generally salutary or deleterious and that modify the risk of progression. EBV denotes Epstein–Barr virus.

PATHOGENESIS

Tissue damage in multiple sclerosis results from a complex and dynamic interplay between the immune system, glia (myelin-making oligodendrocytes and their precursors, microglia, and astrocytes), and neurons (Fig. 4). Although there is debate about whether the root cause of multiple sclerosis is intrinsic or extrinsic to the CNS, studies in animal models, particularly EAE in mice and marmosets, together with analysis of immune cells and their products in CSF and blood of humans, have disclosed a critical role for adaptive immunity.[29] However, despite the fact that some of the disease-modifying therapies that were first shown to ameliorate EAE eventually reached clinical practice, differences between EAE and multiple sclerosis are myriad and have a variety of causes, including the genetic and environmental heterogeneity of humans relative to laboratory mouse strains, as well as a complex immune process in multiple sclerosis that clearly involves T cells (the major driver of EAE) as well as B cells, antibodies, and cells of the innate immune system (as described below). Moreover, although some animal models have clinical progression, none recapitulate the spectrum of critical pathologic features of multiple sclerosis.[33] Genetic data suggest that the pathogenesis of multiple sclerosis shares important features with a variety of non-CNS autoimmune diseases.[34]

Both helper (CD4+) and cytotoxic (CD8+) T cells have been described in multiple sclerosis lesions:

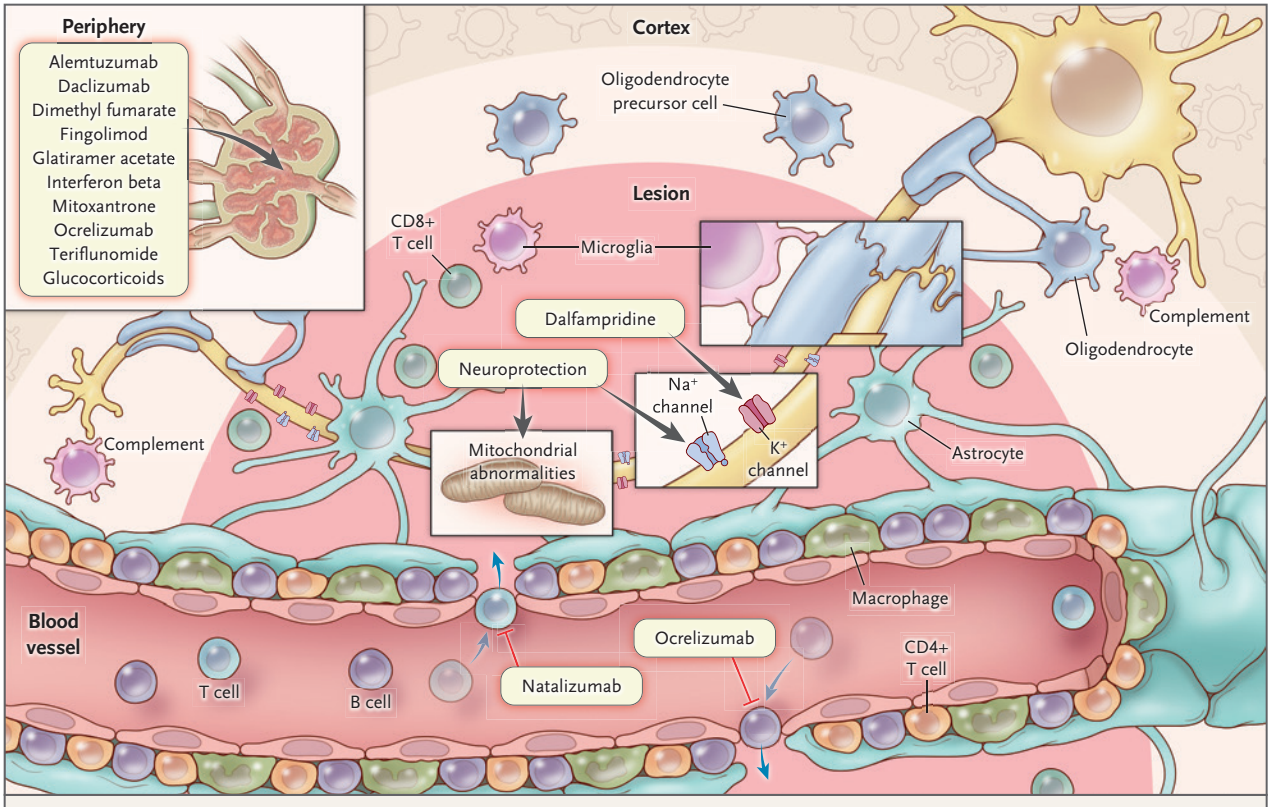

Figure 4. Cells, Molecules, and Therapies.

Shown is a simplified schematic depiction of major cell types within white-matter multiple sclerosis lesions, along with several current and promising therapeutic targets in the central nervous system and in the periphery.

CD4+ T cells are more concentrated in the perivascular cuff, whereas CD8+ T cells are widely distributed within the parenchyma.[35] Drugs that limit T-cell access to the CNS can reduce or eliminate new multiple sclerosis lesions. However, T cells that are reactive to myelin antigens have been observed in similar proportions in people with and people without multiple sclerosis, which suggests either that these cells are dysfunctional in multiple sclerosis or that other immune factors also play critical roles.

Because of the dramatic success of B-cell–depleting antibodies in limiting multiple sclerosis lesion formation and clinical disease activity, there is renewed attention on the role of B cells.[36] It has long been known that the CSF of most patients with multiple sclerosis harbors unique antibodies (oligoclonal bands) that are produced within the CNS. There is evidence that the antibody-producing function of B-lineage cells is important in some multiple sclerosis lesions.[7] However, because of the rapidity of the clinical response to B-cell depletion (as early as 8 to 12 weeks), even before the reduction of circulating immunoglobulin, it seems more likely that other functions of B cells, including antigen presentation to helper T cells and cytokine production, are more relevant.

Cells of the innate immune system are especially important in the pathogenesis of multiple sclerosis.[37] Bloodborne macrophages infiltrate active multiple sclerosis lesions and remove myelin debris and inflammatory by-products; classically and alternatively activated macrophages, as well as mixed populations, have been described in these lesions. Microglia, the primary endogenous phagocytes of the CNS, are abundant in multiple sclerosis lesions, but whether their role is pathogenic or protective — or both — remains uncertain.[38] Microglial activation, often remote from established lesions, has been found in the white matter of autopsy specimens from patients with multiple sclerosis[39] and may represent the earliest stage of lesion development (as is the case in

animal models[40]). Once activated, microglia and macrophages are pathologically indistinguishable, but progress with the use of gene-expression technology has opened the door to unraveling their separate contributions, potentially enabling the development of targeted therapy.[41] Studies in animals have suggested that monocyte and macrophage populations strongly influence myelin regeneration.[13,42]

Disturbance in the blood–brain barrier is an important step in the development of white-matter lesions, which show evidence of gadolinium extravasation on MRI early in their development. Abnormal vascular permeability precedes inflammatory demyelination in EAE[40] and potentially in multiple sclerosis.[43] Studies in mice have shown that leakage of a key plasma protein (fibrinogen),[44] or even secretion of a bacterial toxin,[45] can trigger inflammatory demyelination by a cascade that involves microglial activation and subsequent adaptive immunity. In early multiple sclerosis lesions, vessels near the lesion center become permeable to gadolinium, which then diffuses passively into enlarged interstitial spaces; days later, the central breach in the blood–brain barrier begins to repair, while small capillaries at the lesion edge become permeable — perhaps as part of the early wound-healing process.[46] Leptomeningeal inflammation can also contribute to vascular permeability, but this appears to be a chronic process.[20]

GLIAL-CELL BIOLOGY

Acute multiple sclerosis plaques show activation of astrocytes and microglia and sometimes caspase-independent oligodendrocyte apoptosis.[7] Microglia are prominent in white-matter lesions but are less activated in gray matter.[18] Importantly, microglia play dual roles, sometimes mediating inflammation but in other circumstances promoting repair through clearance of myelin debris.[47] In gray matter, microglia may limit damage through pruning of dysfunctional synapses that express classical complement cascade proteins (C1q and C3). This pruning process may become pathologic if activated astrocytes promote aberrant expression of complement at synapses, thereby accelerating degeneration.[48] Since astrocytes are a major component of the multiple sclerosis plaque, they are well positioned to enhance inflammation by releasing effector molecules, but they may also limit damage by taking up glutamate, providing metabolic support to axons, and maintaining the blood–brain barrier.[49]

An underemphasized but surprisingly common cell (approximately 5% of all CNS cells) is the oligodendrocyte precursor cell, which expresses the proteoglycan NG2.[50] Oligodendrocyte precursor cells can differentiate into oligodendrocytes and are present even late in life,[51] but in patients with multiple sclerosis they are often arrested at the plaque edge, or they may differentiate into premyelinating oligodendrocytes but fail to wrap myelin.[52] Thus, promoting oligodendrocyte precursor-cell differentiation is an attractive strategy to enhance endogenous remyelination, but such a strategy must be balanced against the potential of oligodendrocyte precursor cells to respond to cytokines and thereby participate in inflammation themselves.[53,54] Furthermore, oligodendrocytes may become dysfunctional even without dying, causing tissue damage through loss of trophic support to axons; whether such dysfunctional oligodendrocytes can participate in repair is unclear.

AXON BIOLOGY

Although relative axonal sparing in the face of profound demyelination is a hallmark of multiple sclerosis pathology, axonal transections are frequent, especially acutely.[55] Studies with two-photon microscopy in animal models have begun to elucidate relevant cellular and molecular processes, some of which are potentially reversible.[56] In chronically demyelinated lesions, denuded axons remain vulnerable and can degenerate slowly; possible mechanisms include impaired axonal transport, mitochondrial dysfunction, and increased energy demands related to the upregulation of ion channels.[57] Adaptive immunity — which is critical for the formation of new white-matter lesions — is much less prominent in the slow neurodegeneration of progressive multiple sclerosis, which highlights the importance of glial activation and secondary mechanisms of injury.

BIOMARKERS

MAGNETIC RESONANCE IMAGING

The slow rate of disease progression in time frames that are relevant for clinical monitoring or clinical trials, together with heterogeneous pathogenic mechanisms and the impracticality

of directly sampling CNS tissue (as opposed to blood or CSF), have limited the development of biomarkers for progressive multiple sclerosis. The most important diagnostic and prognostic technique for assessing multiple sclerosis — particularly early in the disease course — is MRI, which is currently the only technique that can interrogate the entire CNS in vivo.

Inflammatory demyelination is easily visible on MRI, as are changes in the blood–brain barrier that accompany its early development. Figure 1 shows the in vivo appearance on MRI of lesions in the periventricular white matter, thalamus and brain stem, spinal cord, and optic nerve. Since 2000, MRI has been the key diagnostic test when patients present with a clinical syndrome that is suggestive of multiple sclerosis, and the most recent criteria[58] — when applied carefully[59] — allow for accurate diagnosis with a single scan. MRI diagnostic criteria are revised as new data accumulate, and standardized protocols for routine use have been proposed.[60,61] MRI is also critical in the development of new disease-modifying therapies, because new lesions are an order of magnitude more frequent than clinical relapses.[62] Indeed, the effect of a therapy on the formation new lesions, as detected by MRI, in small proof-of-concept studies strongly predicts the effect of the therapy on rates of relapse in definitive trials.[63] Furthermore, MRI findings that are consistent with multiple sclerosis have been observed in healthy people who underwent scanning for other purposes (such as research), and clinical multiple sclerosis develops in up to 50% of people with this so-called radiologically isolated syndrome, sometimes with a primary progressive course.[64,65]

Neurodegeneration in multiple sclerosis is best captured on MRI by measuring the size of the brain or spinal cord. An abnormally low brain parenchymal fraction — a measure of brain size relative to intracranial capacity — can be taken as surrogate evidence of previous disease-related atrophy of the brain. In cohort studies, CNS atrophy has been documented even before clinical presentation.[66,67] Atrophy complements lesion-based biomarkers,[68] and proof-of-concept clinical trials using atrophy as the primary outcome have been published.[69,70] Studies of CNS atrophy have focused on specific gray-matter structures (the neocortex and thalamus).[71-73]

Because conventional MRI biomarkers have not shown a strong correlation with clinical status at the population level, probably because of the heterogeneous presentation and course of multiple sclerosis and the inherent variability of clinical measures, there has been a trend toward the use of imaging to investigate multiple sclerosis pathology and pathogenesis, including perivascular inflammation, the development of cortical and spinal cord lesions, myelin loss and regeneration, innate immune activation, leptomeningeal inflammation, and network function.[14] Such research has been facilitated by the advent of 7-tesla MRI and, to a lesser extent, molecular tracers detectable by positron-emission tomography. A particularly exciting innovation has been the use of optical coherence tomography to rapidly assess the retina at micron-level resolution. Retinal ganglion-cell axon loss results in easily detectable retinal thinning, which tracks with MRI changes in the brain[74] and can predict the evolution of disability at the cohort level.[75]

BLOOD AND CSF

Clonal expansion of immunoglobulin-secreting B cells and plasma cells in the CNS results in the characteristic finding of CSF-specific oligoclonal bands.[76] Although the targets of these immunoglobulins are probably multifaceted, their presence implies a CNS-restricted immune response. However, the specificity of oligoclonal bands for multiple sclerosis is poor, and infections can cause the same pattern. Currently, no externally validated blood immune marker has adequate sensitivity and specificity to be used for the diagnosis of multiple sclerosis, which probably reflects the genetic and environmental heterogeneity of the disease. CSF and serum neurofilament light chains are promising in their ability to reflect axonal pathologic processes in the CNS at the cohort level,[77] and there is ongoing interest in various types of noncoding RNA molecules that can affect gene expression.[78] The extent to which these approaches will be useful in patients remains unclear.

THERAPIES

As of December 2017, the Food and Drug Administration has approved 15 medications for modifying the course of multiple sclerosis: 5 preparations of interferon beta; 2 preparations of glatiramer acetate; the monoclonal antibodies

natalizumab, alemtuzumab, daclizumab, and ocrelizumab (the first B-cell–targeted therapy); the chemotherapeutic agent mitoxantrone; and the small-molecule oral agents fingolimod, dimethyl fumarate, and teriflunomide. Dalfampridine has been approved as a symptomatic therapy to improve walking speed. It is beyond the scope of this article to discuss the relative benefits, risks, modes of action, and routes of administration of these various medications (although some targets are shown in Fig. 4), except to say that all are approved for relapsing–remitting multiple sclerosis and reduce, to various extents, the likelihood of the development of new white-matter lesions, clinical relapses, and stepwise accumulation of disability. On the basis of the ability of several of these medications to delay a formal diagnosis of multiple sclerosis after an initial attack, there has been a general move toward early treatment, although, as discussed above, the long-term value of this approach with respect to preventing progressive multiple sclerosis remains uncertain. The recent approval of ocrelizumab for primary progressive multiple sclerosis is a promising step, but the reasons for the ability of ocrelizumab to slow progression[79] remain uncertain. Another important trend has been to escalate treatment with a target of "no evidence of disease activity," as evidenced by the absence of new lesions, relapses, disability progression and, more recently, tissue atrophy[80,81]; however, it is doubtful that multiple sclerosis can be fully arrested with current therapies. Several incipient multicenter studies will compare early intensive treatment with more conventional treatment-escalation approaches.

Small-scale studies have shown that immunoablation followed by autologous hematopoietic stem-cell transplantation may be a highly durable and effective — and increasingly safe — therapy.[82] The favorable side-effect profile and high efficacy of B-cell–inhibiting therapies is likewise a welcome development, although opportunistic infections can occur in rare cases, and postmarketing studies will need to monitor long-term side effects. There are early-stage efforts to interfere with specific T-cell populations that are thought to drive multiple sclerosis, stemming from data indicating that certain key subsets of helper T cells, including those that express both interferon gamma and interleukin-17, are important.[83,84] Such approaches may involve specific inhibition, clonal deletion, or induction of immunotolerance. Previous attempts at targeting cytokines have been unsuccessful[85] or even deleterious,[86] probably because of an incomplete understanding of the roles of different forms of cytokines and their receptors, as well as compensatory pathways. The innate immune system has not been specifically targeted in large-scale trials of treatment for multiple sclerosis, and given the high likelihood that this system can be both protective and deleterious, such efforts must be approached cautiously. Nonetheless, the ubiquity of innate immune cells in and around multiple sclerosis lesions underscores the need for further research.

Beyond the immune system, a great deal of work has revolved around tissue repair and protection. On the repair side, small studies have preliminarily reported mixed results for therapies that promote endogenous remyelination through various pathways.[87] On the basis of preclinical data, including in vitro screens and testing in models such as EAE, several approved drugs (targeting, e.g., nuclear hormone receptor, histaminic, cholinergic [muscarinic], and adrenergic pathways) are being tested for remyelination or myelin protection. Transplantation of neural or oligodendrocyte precursor cells into the brain is effective in animal models, but well-designed clinical trials involving patients with multiple sclerosis have not been undertaken, and it is likely that promotion of endogenous remyelination will prove more fruitful and feasible, especially if the inhibitory factors inherent in the multiple sclerosis plaque can be overcome.[52] A challenge for remyelination trials is the lack of a robust, easily deployable biomarker of success. Visual evoked potentials have been used in small studies, but standardization is difficult and technical variability high. The specificity of high-resolution imaging-based markers for myelin regeneration remains questionable. Nevertheless, MRI is highly sensitive to changes in myelin, and such sensitivity can be exploited in early proof-of-concept trials.[88]

Axonal protection is actively being examined. Results from initial clinical trials of a wide variety of drugs have been published or reported, with several medium-to-large studies currently under way.[89] There is an emerging consensus that slowing the rate of cerebral or spinal cord atrophy is a feasible goal, which, at the proof-of-

concept stage, can be undertaken in several hundred people over a period of a few years.[90] However, definitive proof of neuroprotection — an elusive goal in many neurologic conditions — awaits larger studies with clinical end points.

CONCLUSIONS AND FUTURE DIRECTIONS

Meaningful advances in basic immunology, myelin biology, and neuroscience, together with a global focus on halting progressive accumulation of disability,[91] have opened the promise of a multipronged understanding of, and therapeutic attack on, multiple sclerosis. At the same time, a renewed focus on lesion development and repair — more broadly conceived to include lesions in white matter, gray matter, and leptomeninges — should ultimately unify lines of research, particularly on the side of fluid and imaging-related biomarkers and clinical outcomes, which have sometimes strayed too far from the causative biology. The richest conception of multiple sclerosis will allow appreciation of common pathology, which, in the context of variable triggers and clinical courses, makes multiple sclerosis among the most remarkable of all neurologic disorders.

Dr. Reich reports having cooperative research and development agreements with Vertex Pharmaceuticals, holding a patent (US9607392) on a system and method of automatically detecting tissue abnormalities, and having a pending patent (PCT/US2013/033334) on a method of analyzing multisequence MRI data for analyzing brain abnormalities in a patient; Dr. Lucchinetti, receiving grant support from Novartis, Sanofi-Synthelabo, Biogen, Mallinkrodt, and Alexion; and Dr. Calabresi, receiving grant support, paid to his institution, and consulting fees from Biogen Idec, grant support paid to his institution from Novartis, MedImmune, Teva, and Annexon, and consulting fees from AbbVie, Merck, Vaccinex, Vertex, and Disarm Therapeutics. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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