Multiple sclerosis (MS) is a degenerative neurologic disorder with complex immunopathologic features and multiple subtypes, which may commonly be characterized as either relapsing/remitting or progressive. MS pathology involves non-inflammatory (degeneration of oligodendrocytes) and inflammatory components. The latter, considered the primary pathology, results in development of the hallmark plaques, which contain constituents of the cellular and humoral immune system. This discussion explores the immunopathologic origins of MS and how the immunologic cascade of cellular events relates to disease progression/compensation and the current therapeutic approach.

(Multiple sclerosis (MS) is an inflammatory and degenerative neurologic disorder with complex immunopathologic features and a variable clinical course. The condition is formally categorized into 4 clinical subtypes (Table 1), and is generally characterized by either episodic acute periods of worsening, gradual progressive deterioration of neurologic function, or combinations of both. The majority (approximately 85%) of patients initially present with relapsing/remitting disease, which is characterized by neurologic dysfunction (ie, numbness, weakness, and incoordination), punctuated by intervals of clinical inactivity. The remaining 15% of patients present with primary progressive disease (ie, progressive neurologic deterioration without clinical relapses). Within 10 years of disease onset, almost 50% of patients with relapsing/remitting MS will develop secondary progressive MS, where they will experience neurologic deterioration without additional clinical exacerbations.

The hallmark of MS pathology is the plaque, an area of inflammatory demyelination that, on gross examination, appears as grayish lucencies within otherwise opaque white matter. Histologically, plaques contain constituents of the cellular and humoral immune system (eg, lymphocytes, macrophages, natural killer [NK] cells, and antibodies) and may demonstrate marked heterogeneity. Within active inflammatory MS lesions, axonal transections are common. MS pathology may also involve non-inflammatory degeneration of oligodendrocytes (myelin-producing cells) and neurons. Whether these additional pathologic features in MS are secondary to inflammation or an additional primary process remains a source of debate.

**Immunopathologic Origins**

From an immunopathologic perspective, 4 fundamentally different patterns of demyelination exist (Table 2) and are defined on the basis of myelin protein loss, geography and extension of plaques, patterns of oligodendrocyte destruction, and immunopathologic evidence of complement activation. The most commonly observed lesion in relapsing MS is the type...
II plaque, which is known to contain T/B cells and antibody and complement deposition, and has a typical architecture involving perivenular inflammation (inflammation surrounding veins). Type III and IV plaques have atypical architecture and show additional pathologies, such as oligodendrocyte loss and oligodendrocyte apoptosis. Active research continues to pursue correlations between MS neuropathology and clinical disease subtypes and treatment response, but immediate relationships have remained elusive. In one recent study, all acute plaques have shown a type II phenotype, suggesting that effective therapies should target both T and B lymphocytes.

In examining the pathogenesis of MS, it is useful to model the disorder within 2 basic compartments: the central nervous system (CNS) and the periphery, which are separated by an endothelial barrier (blood-brain barrier [BBB]) that is relatively impermeable to soluble compounds and immune cells. In summary, a cascade of events in the periphery trigger immune cells to differentiate into pathologic (eg, proinflammatory) subtypes that subsequently infiltrate the CNS, causing neurologic damage through multiple mechanisms. The immunologic cascade begins in the periphery (lymph nodes or spleen), where an antigen-presenting cell (APC), in combination with major histocompatibility complex type II, presents an unidentified antigen to an undifferentiated CD4 T cell that can recognize a part (ie, epitope) of the antigenic target. This T cell is then prompted to differentiate in a proinflammatory direction to what is often called a T-helper type (Th1) cell. Th1 cells produce a mixture of proinflammatory cytokines (eg, interferon [IFN] γ and tumor necrosis factor-α), which induce APCs to differentiate in a proinflammatory pathway, upregulate proinflammatory effector T cells, and induce BBB endothelial cells to upregulate adhesion markers on their surface. Proinflammatory T cells also upregulate adhesion markers on their cell surface (eg, very late antigen-4 [VLA-4]) and produce tissue metalloproteases (MMPs) that help break down the BBB. These actions allow Th1 cells to adhere and penetrate the BBB at specific sites of entry into the CNS.

As with most bodily processes, the immune system is governed by a system of checks and balances. Simultaneous to the Th1 proinflammatory response, the immune system will induce T cells to differentiate into a Th2 subtype. Th2 cells produce a different composition of cytokines (eg, interleukin-4, interleukin-5, interleukin-6, interleukin-13, transforming growth factor-β) that, in MS, appear to have anti-inflammatory effects. Th2 cells can cross-communicate with Th1 cells to help maintain a balance between these 2 arms of the immune response. As part of a dual role, Th2 cells can also upregulate the B-cell response, which in turn may have proinflammatory and regulatory functions.

There are other important players in the immune repertoire that contribute to the immunopathology of MS including effector cells (eg, CD8 type T cells, NK cells, monocytes, and macrophages), soluble factors (eg, chemokines and complement), and general mediators of inflammation (eg, mast cells). A variety of these activated immune cells may enter the CNS, where they participate at various levels in the disease...
process. Th1 CD4 T cells that enter the CNS reenact immunological responses, which results in recruitment of B cells, effector T cells, and macrophages, which in turn causes tissue damage via cell-mediated cytotoxicity, complement-mediated lysis, opsonization, and production of nitrous oxide, free radicals, and proteases. Th2 CD4 cells may enter the immune system and suppress this proinflammatory response, which is known as bystander suppression. B cells within the CNS may produce antibodies that may cause direct damage through complement activation or antibody-dependent, cell-mediated cytotoxicity. B cells may also act as APCs and present antigen to T cells. Certain types of T cells (regulatory T cells) and NK cells may have a profound effect on proinflammatory T-cell populations, resulting in an additional layer of regulatory control.

Disease Progression and Compensation

Although MS is often classified into relapsing or progressive subtypes, it is understood that disease activity is continuous, with irreversible damage that occurs during the disease process. Sequential, monthly magnetic resonance imaging (MRI) of patients with clinically silent MS demonstrates development of new lesions that may appear and then disappear over time, despite an absence of clinical relapses. Active lesions may cause both myelin and axonal injury. MRIs reveal ongoing damage even within normal white matter outside of lesions.

In studies examining patients at the time of a first clinical attack, specialized MRI protocols (eg, MR spectroscopy) of the whole brain or normal-appearing white matter reveal imperfect neuronal health. In one study, levels of neuronal aspartyl acetate, a chemical signature of neuronal metabolic health, were found to be significantly reduced in patients with a single clinical attack (otherwise known as clinically isolated syndrome [CIS]). Some patients may not show clinical disability at this stage, despite ongoing inflammation, because normal areas of the brain are recruited to help complete simple tasks. In a functional MRI study of brain activation, researchers asked patients with CIS to perform a simple repetitive finger flexion-extension task and then identified areas of the brain with increased blood flow. Investigators found that multiple areas outside of the contralateral motor cortex were recruited for task performance in patients with CIS, compared to controls. These data suggest that neuronal recruitment is used as an adaptive mechanism to limit the functional impact of demyelinating injury.

Therapeutic Approach

As a result of compelling evidence indicating disease progression in the absence of clinical relapses, the mantra of current immunomodulatory therapy is to treat early in order to prevent inflammatory injury from occurring (see article by Melody Ryan, PharmD, MPH, BCPS, CGP, for more information on MS treatment). Currently, 5 approved immunomodulatory therapies (3 IFN products, glatiramer acetate, and natalizumab) are available for the treatment of relapsing forms of disease, and all of these agents act only in the periphery (Figure). Although it is unclear exact-
ly how they function in our current paradigm of MS pathogenesis, it is thought that IFNs affect multiple levels of the immune response. First, they reduce antigen presentation by downregulating major histocompatibility complex class II expression on APCs. Second, they limit costimulatory molecule expression on T and B cells. Third, they reduce BBB injury by downregulating MMP expression. And finally, they induce the production of soluble VLA-4, which competes with activated T cells for receptors on the endothelial surface.

Glatiramer acetate is thought to modulate the antigen presentation process in the direction toward the Th2 pathway. This likely occurs through modulation of APC differentiation, with the ultimate effect being suppression of the Th1 pathway in the periphery and bystander suppression in the CNS. Natalizumab, a monoclonal antibody directed against VLA-4 adhesion molecule, interferes with the migration of both T and B cells into the CNS. Natalizumab may also have additional effects on immune cell activation.

In regard to therapeutic efficacy, studies have shown that both IFNs and glatiramer acetate are more effective in reducing new attacks in patients with CIS versus those with long-standing MS.\(^{13-19}\) It is, therefore, critical that physicians initiate therapy early on in the disease process, when treatment has a better possibility of optimizing therapeutic outcomes and preventing irreversible neurologic injury. Delaying treatment not only impacts progression from CIS to MS, but it also appears to have a significant effect on cumulative disability over the course of the disease. Research has shown that in patients who have a significant lesion load on MRI or multiple neurologic symptoms at the time of the first attack, delaying treatment for 2 years (vs treating immediately) results in a significantly higher disability score by the third year.

In the immediate future, there are promising treatments for MS that have novel mechanisms of action. Fingolimod is an oral agent that inhibits exit of immune cells from lymph nodes. Cladribine is an oral agent that specifically suppresses lymphocytes, and alemtuzumab is a monoclonal antibody that results in significant immune cell suppression. Daclizumab is an antibody that binds to the interleukin-2 receptor and modulates an important population of regulatory NK cells. Rituximab is a monoclonal antibody that eliminates naïve and memory B cells. Additional therapies, such as bone marrow transplantation, are also under investigation for highly aggressive disease.

**CONCLUSIONS**

Multiple sclerosis is a complex, inflammatory neurologic disease with diverse pathologic and clinical features. The inflammatory activity may result in subtle symptoms that may escape detection in the absence of vigorous probing. Current therapeutics work best in the more active inflammatory phases, which occur early in the disease course. Therefore, optimizing immune therapy during the inflammatory phase offers the best opportunity for delaying, mitigating, and perhaps preventing progressive MS.

**REFERENCES**