Biology of Demyelinating Disease, a lecture given by Saud A. Sadiq, MD, on March 11, 2006, at the Columbia University College of Physicians and Surgeons 29th Annual Postgraduate Review Course in Basic and Clinical Neurosciences.

Summary

The neuron is capable of conducting signals rapidly across vast distances. Myelin, the lipid-protein molecules that coats the neuronal axon, greatly facilitates rapid neuronal communication. The devastation caused by the destruction of myelin leads to devastating symptoms. In this lecture, Dr Saud A. Sadiq examines the pathophysiology of demyelinating disorders, focusing on the most common of these disorders, multiple sclerosis. He explores how a cascade of immune responses culminates in full-blown multiple sclerosis.

Multiple sclerosis usually affects young adults, with women two to three times as likely to contract it as men worldwide. Subclinical changes precede the onset of symptoms. Most patients present during the inflammatory phase of the disease, which later progresses to a neurodegenerative phase characterized by the destruction of myelin. Pathologically, multiple lesions are visible, some older some younger, and it is this multiplicity of lesions which gives the disorder its name. Spinal fluid examination reveals that 90% of MS patients exhibit oligoclonal bands, which suggests immune hyperactivity or aberrations. Genetic factors also play a role in MS; the geographic areas with the highest concentrations of MS are North America and Europe. Further evidence of genetic susceptibility comes from the high incidence of MS within families: 20% of patients have a positive family history.

Although MS is the most common disorder and the focus of Dr Sadiq's lecture, he carefully notes that there are many other demyelinating disorders that may present with similar white-matter lesions revealed by MRI. Clinicians must be aware of these other disorders, such as acute disseminated encephalomyelitis.

In order to understand what happens in demyelinating disorders, Dr Sadiq first describes the normal structure and function of myelin. With a composition of 75% lipid and 20-25% protein, myelin is a membrane with one of the highest lipid concentrations in the body. While some proteins are present in all types of myelin, other proteins that make up myelin are distinct in the central and peripheral nervous systems. This distinction explains why some disorders primarily affect the peripheral or central nervous system and why a single repair strategy will fail to improve all demyelinating disorders. Structurally, normal myelin is quite compact. In disorder this compact structure unravels.

Myelin aids not only in the conduction of action potentials, which is well known, but also plays a role in metabolism, ion transport, and even modulates the maturation and survival of axons. Thus, the destruction of myelin not only disrupts the conduction of neuronal signals but can lead to the death of the axon itself. This axonal loss is the principal cause of the disability associated with MS.

After outlining the structure and function of myelin, Dr Sadiq describes the pathogenesis of MS. Given a genetic predisposition, often under conditions of chronic stress or hormonal turbulence, a patient will react with an aberrant immune response to a trigger, such as a common virus. This immune response leads to the activation of T cells. At this point the patients are unaware that they now have a susceptibility to MS. Normally, patients present only after the development of inflammatory phase. As Dr Sadiq notes, the hope of developing effective treatment lies in identifying these subclinical changes before the disease has progressed too far.

As the patient moves into the inflammatory phase of the disease, the blood-brain barrier is disrupted and immune cells upregulate the trafficking of lymphocytes across the barrier. The exact mechanisms of the disruption have not been fully elucidated, although Dr Sadiq describes several physiologic changes that may be involved. Inflammatory T cells initiate further immune cascade activation. Ultimately, the most damaging event in the cascade is macrophage activation. Microglial cell activation releases free oxygen, free radicals, and proteases that actually consume the myelin. Unchecked, demyelination almost always leads to axonal loss, which is the cause of the irreversible damage of MS. Arresting the disease in the inflammatory phase offers the only hope of preventing the devastating and irreversible changes of the neurodegenerative phase.

Today, no myelin repair or regeneration strategy exists to reverse the destruction caused by MS. Yet exciting breakthroughs loom on the horizon. As Dr Sadiq describes, current research is dedicated to finding ways to repair and regenerate myelin. A new medication, natalizumab, blocks white cells as they try to cross the blood-brain barrier. Other trials are looking into certain genes that may aid in neural stem cell development for oligodendroglial cell repair and regeneration. A comprehensive approach would provide growth factors, inhibition of glial cells, as well as stem cells infusions. Dr Sadiq concludes the lecture with careful optimism that the future of MS treatment lies in these and other studies that offer a glimmer of hope in the face of this devastating disorder.