New treatment advances in multiple sclerosis

Spotlight on Palmetto Health-USC Pediatric Neurosurgery

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As physician co-leaders of Palmetto Health’s neuroscience service, we share a vision to provide the most advanced neurology and neurological surgery treatments available to the residents of South Carolina. We are excited to share this edition of our neuroscience journal featuring articles about new treatment advances in multiple sclerosis and our pediatric neurosurgery practice.

Souvik Sen, MD, MS, MPH
Chair of Neurology, Palmetto Health-USC Neurology
Professor of Neurology, University of South Carolina School of Medicine

Roham Moftakhar, MD
Chief of Neurosurgery, Palmetto Health Richland
Medical Director, Palmetto Health-USC Neurosurgery
Associate Professor of Clinical Surgery, University of South Carolina School of Medicine
Meet our newest physicians

Ravish A. Kothari, MD
Neurologist
Palmetto Health-USC Neurology

Ravish Kothari, MD, received his medical degree from Government Medical College, Bhavnagar, in Gujarat, India. He completed a residency in neurology and a fellowship in vascular neurology at Palmetto Health/USC School of Medicine. Dr. Kothari is board certified in neurology. Specializing in neurology and vascular neurology, Dr. Kothari joins our team of stroke neurologists.

Andrew M. Price, MD
Neurointensivist
Palmetto Health-USC Neurosurgery

Andrew Price, MD, received his medical degree from the West Virginia University School of Medicine in Morgantown. He completed residencies in internal medicine and neurology at Temple University Hospital in Philadelphia, and a fellowship in neurocritical care at Duke University in Durham, North Carolina. Dr. Price is board certified in neurology. Specializing in neurology and neurocritical care, Dr. Price joins our team in the Neuroscience Intensive Care Unit (NSICU).
Multiple sclerosis (MS) is an immune-mediated demyelinating disorder of the central nervous system. This chronic disease is categorized into patterns of acute symptom onset and remission, with or without chronic progression of associated disabilities. MS is the most common demyelinating disease in high-income countries, and the most common cause of disability in young adults. Prevalence is highest in North America and Europe, at 140 and 108 per 100,000, respectively. According to the National MS Society, in the United States, approximately one million people suffer from this condition, a number which has increased in the past few decades, where it was previously only 300,000. It mainly affects younger Caucasian adults between the ages of 20 and 50, with a female to male predominance of 3:1. Other ethnic groups suffer from the condition, as well. Genetic and environmental risk factors each play a role in disease manifestation. A multitude of environmental factors have been explored, with the strongest evidence supporting links with smoking, anti-EBNA IgG sero-positivity and infectious mononucleosis. High latitude also carries a positive association with MS. Recent research has connected this environmental factor with decreased vitamin D as a result of low sun exposure. Fifty-percent of individuals with MS have a positive family history for the disease, often with one or more family members affected. Additionally, identical twins of those affected have a one-in-three chance of developing the disease. Genetic susceptibility has been demonstrated in individuals with major histocompatibility complex (MHC) alleles. Interestingly, this includes HLA-DRB1, a gene which has been shown to express alleles containing a vitamin D response element.

The exact pathophysiologic etiology of MS is unknown, and the mechanism is not fully understood. Generally, the mechanism is characterized by central nervous system tissue damage caused by immune mediated inflammation, leading to demyelination and subsequent axonal degeneration. Possible autoimmune epitopes have been identified, including myelin basic protein. On a cellular level, MS has classically been associated with T lymphocytes, specifically the T helper 17 cells. These cells are frequently found in MS plaques,
as well as in the cerebrospinal fluid (CSF) and peripheral circulation.\textsuperscript{5} The role of B lymphocytes in MS pathophysiology has been increasingly explored, as new MS drugs specifically targeting B lymphocytes have shown promising results in recent studies.\textsuperscript{6–8}

The clinical manifestations of MS depend on the location and severity of a given inflammatory lesion or lesions. Often, patients will initially complain of blurred vision or a focal neurologic deficit, while later complaints may present as cognitive difficulties and urinary incontinence. Diagnosis of MS is made with magnetic resonance imaging (MRI) of the brain and spinal cord, which will show specific distributions, such as Dawson finger-like projections in the periventricular white matter, as well as juxtacortical and infratentorial lesions. Some of these lesions may be enhanced with gadolinium, which would demonstrate active disease. CSF studies may show elevated protein, cell count, IgG index, and oligoclonal bands.

The disease course varies from patient to patient. There are three types, including relapsing-remitting, primary progressive and secondary progressive. The relapsing-remitting is the most common type, and presents as an acute clinically isolated syndrome that remits, leaving no or minimal persistent disability. Later, disability accumulates, which defines the clinical syndrome of secondary progressive. The primary progressive type presents initially with acute flares and persistent residual disability from the onset that continues to progress indefinitely.\textsuperscript{9}

The basis of MS treatment is to decrease inflammation via immune modulation. Therefore, the goal of these medications is to decrease the annualized relapse rate (ARR) by decreasing number of relapses, accumulation of disability, and MRI CNS lesion load. The desired endpoint is the achievement of “NEDA,” or No Evidence of Disease Activity. This is marked by no new, enlarging or enhancing lesions on MRI, no relapses, and no progression of disability. To this point, no medication has achieved NEDA.

All MS medicines render patients susceptible to common as well as rare infections. They may also carry a slight increased risk for developing cancers compared to the general population.

The classical treatment for MS is \textit{interferon-ß}, an immune modulator that suppresses T cell activation. Side effects include flu-like symptoms, and blood count (CBC) and liver function (LFT) need to be monitored, as they are with all other MS drugs. \textit{Glatiramer acetate} is another injectable drug that does not require such monitoring. Injection site reactions are common with this drug. Oral drugs, including \textit{fingolimod}, require first dose observation due to possible bradycardia and precipitation of heart block. Periodic eye check-up is necessary due to macular edema. \textit{Dimethyl fumarate} requires PPD and VZV titer prior to administration, as its mechanism predisposes patients to infection with tuberculosis and herpès. It also may result in progressive multifocal leukoencephalopathy (PML), a disease caused by the John Cunningham (JC) virus in the immunologically suppressed. \textit{Teriflunomide} is an oral agent that is a category X teratogen that should not be given to men or women of reproductive age who are attempting to have children, as it has been found in semen and other tissues for up to two years after the last dose.

\textit{Natalizumab} is an intravenous (IV) infusion given every 28 days. More than 750 cases of PML have occurred with natalizumab, compared to about 20 cases with fingolimod and 5–10 with dimethyl fumarate. \textit{Alemtuzumab} is an infusion given for five days and repeated one year later for three days; however, it requires close monitoring for up to four years from the last
dose due to autoimmune side effects that may lead to thrombocytopenia, glomerulonephritis and thyroid storm. **Decluzumab** is another drug that has been removed from the market due to incidence of autoimmune hepatitis.

**Ocrelizumab** is a newer MS drug. It is a fully humanized monoclonal antibody targeting CD20+ B lymphocytes. It is given as an IV infusion every six months. Side effects include infusion reaction, which requires close monitoring for a period of time due to the frequency of occurrence. In this author’s practice, many patients have reported recovery from prior disabilities, with some regaining functions such as the ability to walk with assistance from previous wheelchair-bound status. While post-marketing research for ocrelizumab is still ongoing, early results from the phase II trial demonstrated an annualized relapse rate (ARR) of 80 percent over 24 weeks. This number can be compared to approximately 68 percent for natalizumab, approximately 33 percent for injectables, and approximately 42 percent for oral medications. Additionally, the OPERA I and OPERA II trials demonstrated a 46 percent and 47 percent lower ARR with ocrelizumab compared to interferon β-1a.

Perhaps more interestingly, ocrelizumab has proven to be a promising drug in the setting of primary progressive MS, a disease process which has limited options for disease modification. In the Oratorio trial, ocrelizumab was shown to have a statistically significant decrease in disability progression at 12 weeks as a primary endpoint (32.9 percent vs 39 percent with placebo), and at 24 weeks as a secondary endpoint (29.6 percent vs. 35.7 percent with placebo). Also noted was a change from baseline on timed 25-foot walk of 38.9 percent with ocrelizumab compared to 55.1 percent at 120 weeks with placebo. With ocrelizumab, MRI CNS lesion load decreased by 3.4 percent, compared to 7.4 percent with placebo. Ocrelizumab also demonstrated a brain volume decrease of 0.9 percent, compared to brain volume decrease of 1.0 percent with placebo.

Medications currently being developed include ozanimod, siponimod and ibudilast. High-dose biotin was also explored as an option, however it has since been removed from the European market.

Overall, since interferon-1β was first approved in the early 1990s, MS treatment has progressed significantly. New pharmacological targets have led to successful disease modification, while also advancing the fundamental understanding of the pathophysiological mechanism of the disease itself. Continued research into new drugs based on recent successes of drugs like ocrelizumab carries great optimism for the future of MS treatment.

**References**

**Spotlight on**
**Palmetto Health-USC**
**Pediatric Neurosurgery**

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Columbia, SC 29203

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Phone: 803-434-2700
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**Our care team**

**Stanley O. Skarli, MD, FAANS, FACS, FAAP**
Neurosurgeon, director of Pediatric Neurosurgery, Palmetto Health-USC Neurosurgery, associate professor of surgery, University of South Carolina School of Medicine

**Medical Degree** Oral Roberts University School of Medicine in Tulsa, Oklahoma

**Residency** University of Maryland Medical System in Baltimore

**Fellowship** Primary Children’s Medical Center at the University of Utah in Salt Lake City

**Board Certified** Yes, Neurological Surgery and Pediatric Neurological Surgery

**Specialty and Research Interests** Neuroendoscopy, spinal instrumentation, endoscopic craniosynostosis surgery, craniovertebral junction anomalies and selective dorsal rhizotomy for patients with cerebral palsy

**Spina Bifida Clinic**
Dr. Skarli piloted the Spina Bifida Clinic in the fall of 2016, which has been successful for both families and physicians. The clinic helps streamline the complex care of spina bifida patients typically needing to see multiple practices as part of their care. Patients may be seen by orthopedic surgery, urology and pediatric neurosurgery providers in the same day.
Catherine McClung Smith, MD
Neurosurgeon, Palmetto Health-USC Pediatric Neurosurgery, assistant professor of surgery, University of South Carolina School of Medicine
MEDICAL DEGREE Morehouse School of Medicine in Atlanta, Georgia
RESIDENCY Saint Louis School of Graduate Medicine in St. Louis, Missouri
FELLOWSHIP Children’s Hospital of Colorado in Denver
BOARD ELIGIBLE Yes, Neurological Surgery and Pediatric Neurological Surgery
SPECIALTY AND RESEARCH INTERESTS Surgical treatment of pediatric epilepsy and functional disorders, traumatic brain injury, clinical outcomes and guidelines in a pediatric population

Plagiocephaly Guidelines
Dr. McClung Smith participated in the writing of the “Plagiocephaly Guidelines,” which was published by Neurosurgery in 2016. The guidelines help guide intervention in patients with positional plagiocephaly. She also was a topic editor for the September 2018 Journal of Neurosurgery Focus, which was dedicated to pediatric functional neurosurgery. In addition to providing care for her patients, Dr. McClung Smith is dedicated to the advancement of pediatric neurosurgical care through clinical research.

The “Plagiocephaly Guidelines” can be accessed at: https://www.cns.org/sites/default/files/guideline-pdf/summary_with_recommendations_final_12.1.16.pdf

The September 2018 Journal of Neurosurgery Focus can be accessed through the Journal of Neurosurgery online: https://thejns.org/focus/view/journals/neurosurg-focus/45/3/neurosurg-focus.45.issue-3.xml

Brandi Martinez, APRN, FNP-BC
Advanced Practice Provider, Palmetto Health-USC Pediatric Neurosurgery
EDUCATION University of South Carolina
BOARD CERTIFIED American Nurses Credentialing Center
SPECIAL INTEREST Hydrocephalus

Hydrocephalus Support Group
Brandi Martinez, APRN, FNP-BC, has started a support group for hydrocephalus patients in the Columbia area. The Hydrocephalus Support Group meets once every three months in the Derrick Classroom of Palmetto Health Children’s Hospital. If interested, please contact the Pediatric Neurosurgery office at 803-434-2700.
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