A Multifaceted Look at Multiple Sclerosis

More than 400,000 individuals in the United States and some 2.5 million around the world have been diagnosed with multiple sclerosis, according to the Multiple Sclerosis Foundation. While significant progress has been made in treatment breakthroughs and research discoveries of this chronic, unpredictable disease over the last 60 years, the cause and cure for MS remain elusive. Undeterred, the clinicians and scientists at the Columbia Multiple Sclerosis Clinical and Research Center at NewYork-Presbyterian/Columbia University Medical Center and the Judith Jaffe Multiple Sclerosis Clinical and Research Center at NewYork-Presbyterian/Weill Cornell Medical Center are committed to enhancing the quality of life of patients with MS. Their shared goal is to develop safe and more effective disease-modifying and symptomatic treatments and continue basic and clinical research efforts to understand the disease process and define new therapeutic interventions.

Advancing Clinical Care

NewYork-Presbyterian, through the Columbia Multiple Sclerosis Clinical Care and Research Center, under the direction of Claire S. Riley, MD, and the Judith Jaffe Multiple Sclerosis Clinical and Research Center, directed by Timothy Vartanian, MD, PhD, provide the full range of diagnostic, treatment, and research efforts to address MS and related disorders in both adult and pediatric patients. Here neurologists, neuropsychologists, ophthalmologists, rehabilitative specialists, and pain management specialists provide expertise in the physical, cognitive, emotional, and rehabilitative needs of patients and provide support and resources for their families. The programs also provide patients with opportunities to participate in clinical trials examining the effectiveness of drugs in limiting disease progression and restoring physiologic function in MS.

“The initial phase of multiple sclerosis is characterized by clinical attacks that can involve any neurologic system,” says Dr. Vartanian. “These exacerbations can last weeks to months, with partial or complete recovery. If not treated, the disease will worsen in most patients, generally with a slow and relentless progression of symptoms. Some 15 percent of patients are diagnosed with primary progressive multiple sclerosis, which is characterized by worsening neurologic function from the onset of symptoms without early relapses or remissions.”

“When people ask me about the symptoms of MS, it is a bit of a loaded question,” adds Dr. Riley. “Every function of the nervous system requires myelin, so any of its manifold functions can be disrupted by the disease. The most common form – relapsing-remitting MS – is characterized by symptoms of neurologic dysfunction that evolve over a few hours or days, hang around for a few weeks, and tend to improve spontaneously. That improvement can be hastened with treatment that usually involves corticosteroids to help reduce inflammation.”

According to Dr. Riley, the natural course of these symptoms is to resolve. “If someone is complaining of neurologic symptoms that persist for weeks but then begin to resolve spontaneously, a diagnosis of MS could be considered,” she says. “Typically, symptoms in patients with relapsing-remitting MS will subside completely about 70 percent of the
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future determination of the presence of cognitive decline.”

As part of NeuroNEXT, NewYork-Presbyterian is participating in
a clinical trial of ibudilast, a phosphodiesterase inhibitor for treat-
ment of primary and secondary progressive MS. “This experimental
drug is given to people with primary and secondary progressive forms
of the disease in which there’s no established or proven immuno-
therapy for slowing it down,” says Dr. Riley.

The Challenge of Cognitive Impairment

Studies have shown that 40 to 70 percent of patients with MS
are cognitively impaired. “That means approximately half of the
people with MS will at some point during their disease course
encounter cognitive issues,” says Victoria M. Leavitt, PhD, a clinical
neuropsychologist and researcher with the Columbia Multiple Sclerosis
Center. “For many people this occurs very early in the disease course
and can happen even before physical disability becomes apparent.”

Dr. Leavitt seeks to understand cognitive impairment and lifestyle factors that protect against cognitive decline and identify areas of strength and weakness to guide treatment, provide recommendations, and monitor change over time. She is currently recruiting patients for a longitudinal assessment of cognition in patients with MS funded by the National Multiple Sclerosis Society.

“Cognitive issues can be very isolating and very personal for
individuals with MS because they aren’t as obvious as the physical
symptoms,” says Dr. Leavitt. “If you wake up in the morning and
your left leg doesn’t work, it’s clear you are unable to go to work.
But if you wake up and your memory is a little off, or your ability
to multitask is a little less sharp and you feel it and know it, that’s
a more challenging struggle.”

According to Dr. Leavitt, cognitive impairment has been
recognized as a key symptom of MS for the last 25 years. Prior
to that it was not recognized as a component of MS and, indeed,
actively disputed to have any involvement. “Now that we have
years of research supporting the existence of cognitive impairment, it
is very validating for people,” says Dr. Leavitt. “By evaluating
patients’ cognition early on, we have a baseline that is essential for
future determination of the presence of cognitive decline.”

Dr. Leavitt’s clinical work informs her research. Her goal is to
understand the neural basis of cognitive impairment in MS in ways
that can help target neural structures for behavioral treatment and
pharmacological interventions. “We know that patients with MS
have a varying load of lesions and atrophy in their brain, but the
amount of lesions and atrophy corresponds weakly to the degree
of cognitive impairment exhibited,” continues Dr. Leavitt. “So we
have applied Dr. Yaakov Stern’s theory of cognitive reserve to MS.”

Dr. Stern, a noted Columbia neuropsychologist, theorizes that how
people use their brain over the course of their lives – with a focus
on IQ and education – may provide protection against disease and
actually slow the rate of cognitive decline.

“If you use the brain in a flexible manner and encourage neural
flexibility are important as well,” notes Dr. Leavitt. “I tell patients
to think about their brain as a collection of roads and highways.
If one of the main highways is shut down and you have the ability
to flexibly change pathways, then you’ll do better. We believe that
over a lifetime of intellectually stimulating activities, using the
brain in ways to encourage that neural flexibility is the actual key.”

Wendy S. Vargas, MD, program leader for the Pediatric MS
and Neuroimmunology Program at Columbia, is one of a small
number of pediatric neurologists with subspecialty training in
MS and other demyelinating diseases. “We know that children
with MS tend not to be affected early on with motor problems;
their disability is with cognition,” says Dr. Vargas, who has been
awarded a grant by the National MS Society to study the impact of
cognitive dysfunction in schoolchildren with MS.

“To determine if we can correlate cognitive dysfunction with
brain atrophy, we are comparing standardized records and tests,
school scores, and report cards, with results of neuropsychological
tests and MRI findings,” explains Dr. Vargas. “If the deeper
structures in the brain are affected, then the pathways leading to
the cortex will likely be involved. It is important to map out these
pathways to try to identify which areas of the brain are affected by
MS. Surprisingly, there is very little work being done in this area,
but it is much needed.”

Leading Breakthrough Research

Dr. Timothy Vartanian’s laboratory at the Brain and Mind Research
Institute at Weill Cornell Medicine has made groundbreaking
discoveries in central nervous system remyelination, novel mecha-
nisms of axonal degeneration and regeneration, and mechanisms of
immune-mediated injury to myelin and axons in multiple sclerosis.
The lab’s research interests center on regeneration of the myelin
interneuron in multiple sclerosis, preventing axonal and neuronal injury, and defining the complicated interactions between the immune and nervous systems.

“There are several aspects of MS that we simply don’t quite understand yet,” says Dr. Vartanian, a leading authority on neural regeneration. “We have the most knowledge about the role of the peripheral immune system in the relapsing phase of the illness. We understand it enough that very specific drugs have been designed that limit relapses. The problem is that limiting relapses doesn’t cure the disease. While the very potent medications used currently can dramatically reduce relapses as well as the appearance of active contrast-enhancing lesions on MRI, disability continues to accumulate. Our efforts at Weill Cornell are focused on what we believe to be the two most important, unaddressed questions in MS: How does the disease start and why do patients progress? I would postulate that the disease begins when the first MS lesion forms in the patient. I would further say that the mechanism by which that first lesion forms is exactly the same as the way all truly new lesions form.”

Examining the risk factors for MS, Dr. Vartanian points to studies of identical twins. “If one identical twin has MS, about 20 percent of the time the other twin will have MS, meaning that the disease is 20 percent genetic,” he says. “It also means that about 80 percent can be attributed to environmental factors. Is the environment simply contributory to making the disease worse, or is an environmental agent required for MS lesions to form, that is, for MS to occur in the first place?”

“Not only is environment important and contributory, but environment is necessary for the disease to occur,” says Dr. Vartanian. “One can have a genetic background – that 20 percent risk factor – but you need this environmental trigger. Remembering that all new lesions – truly new lesions – are the same, then whatever the environment is doing must be playing some role in new lesion formation. So, then we have to ask the question, what do we know about new lesion formation?”

The answer is very little, says Dr. Vartanian. “MS is a chronic illness, but people rarely die from it. Therefore, the pathology that we are able to study when a person has donated their brain to science might be months, years, or decades old. The problem is that as time goes on, macrophages clear up that tissue, which is all part of the evolution of the lesion.”

In 1986, a study by Dr. Timothy Murrell, an internist in Australia, suggested that MS seems to occur where there is an abundance of sheep. He identified *Clostridium perfringens* epsilon toxin as a possible causative agent because it creates a multifocal white matter disease in farm animals with striking resemblance to the lesions of MS. “It was known at that time that epsilon toxin would bind to the blood-brain barrier,” says Dr. Vartanian. “Dr. Murrell had this epidemiologic idea that very much supported the notion that epsilon toxin could be a potential MS trigger in humans.”

To explore this hypothesis further, Rashid Rumah, MD, PhD, and Jennifer Linden in Dr. Vartanian’s lab and their collaborator Vincent Fischetti, PhD, at The Rockefeller University studied MS patients for the presence of epsilon toxin. Rashid Rumah was the first to detect the presence of antibodies against epsilon toxin in MS patients, and he along with Jennifer Linden were the first to identify and isolate a *Clostridium perfringens* type B strain in humans. “Humans have never been reported to have the epsilon toxin-producing strains of *Clostridium perfringens*, which are the type B and the type D strain. Fifty percent of humans have the type A strain, but should not have type B or D in them. So, this was very, very interesting to us,” says Dr. Vartanian. “That we identified evidence for the presence of this bacterium in a human is important enough, but the fact that it is present in MS patients is truly significant because the toxin targets the exact tissues damaged during the acute MS disease process.”

The Vartanian lab then went on to test their hypothesis that the environmental trigger for MS lies within the microbiome, the ecosystem of bacteria that populates the gastrointestinal tract and other body habitats of MS patients. “The big question that we all want to answer is, can we find evidence of the toxin in people with MS? That’s the study we’re currently undertaking,” says Dr. Vartanian. “We’re designing a strategy in which we can detect an actual toxin in human samples. Part of that means creating a reagent that can see the toxin and that combines to the toxin. We have spent the past year and a half creating monoclonal antibodies directed against the toxin, and we think we have one now that works well. We already have IRB approval and two major studies designed to enroll patients and healthy controls to look cross-sectionally for the presence of the toxin.”

In other research Dr. Vartanian and his team are investigating failure of remyelination, which is largely responsible for sustained neurologic symptoms in MS. They have identified possible approaches to improving remyelination by blocking hyaluronan deposits that...
inhibit oligodendrocyte precursor cell (OPC) maturation, although the mechanism behind this inhibition is unclear.

“Inhibitors of Toll-like receptor 2 and its signaling pathway have been shown to be effective in blocking hyaluronan inhibitory effects, resulting in enhanced OPC maturation in vitro,” says Dr. Vartanian. “Approaches like these will be of great importance in developing treatments for impaired remyelination in MS.” As evidence for this, recent research conducted by Yinghua Ma, PhD, in the Vartanian lab has identified a drug that potently induces remyelination in mouse CNS tissue. In a highly collaborative effort among Drs. Gauthier, Vartanian, and Ma, the research team is planning their first study to promote remyelination in people with MS. “Because the drugs we are testing already have FDA approval for other disease, we can skip Phase I safety studies and move directly into Phase II or proof-of-concept studies, significantly lessening the time from drug discovery to impact on patients. At the Weill Cornell MS Center, there is definitely the atmosphere of moving as quickly as possible from bench to bedside.”

Anatomy of a Lesion

According to Susan A. Gauthier, DO, MPH, Director of Clinical Research at the Judith Jaffe Multiple Sclerosis Clinical and Research Center, the most important question in MS currently is why patients move into the progressive stage of the disease. “My focus is on imaging myelin in order to understand the factors that lead to myelin destruction in MS,” says Dr. Gauthier. “We know it’s an immune response, but are there certain factors that cause more destruction than others? And are there factors that lead to more repair or less repair?”

The two main hypotheses on why people progress, explains Dr. Gauthier, are 1) years of demyelination leave the axons vulnerable to degeneration, and 2) chronic activation of immune cells, called microglia, within the brain, can be toxic to the neurons. “The research tools we use to investigate these theories include MRI-based myelin-water fraction imaging, which allows us to quantify myelin in white matter and follow it over time, and positron emission tomography (PET) to label microglia or the immune cells in the brain,” says Dr. Gauthier. “We are combining our imaging tools to dissect down into the lesion to acquire information which can be utilized to develop novel treatment targets for both remyelination and myelin protection. Our goal is to identify potential mechanisms that will decrease the amount of myelin damage and/or stimulate myelin repair within lesions.”

Dr. Gauthier’s PET studies examine the role of inflammation due to the immune cells within the MS patient brain. “There is potentially good inflammation and bad inflammation,” she says. “For years we thought all inflammation was bad, but it’s not. All of our treatments are targeted toward the peripheral immune system; however, it’s the immune system within the brain that might actually have a much more influential role in myelin repair or alternatively lack of repair.”

Dr. Gauthier, in collaboration with Weill Cornell physicist, Yi Wang, PhD, has utilized a novel MRI technique called quantitative susceptibility imaging (QSM) to identify that iron deposition is occurring early in MS lesions. “We are finding that many neurodegenerative diseases have increased iron deposition early on within the brain,” notes Dr. Gauthier. “We are exploring the influence of iron deposition in MS lesions on myelin content six or 12 months later to determine if iron causes more myelin damage. There is evidence to suggest that iron with MS lesions may lead to chronic inflammation, which can cause continued damage to the myelin and loss of nerve cells. Understanding the role of iron within lesions may lead to new therapeutic targets.”

(continued on page 6)
NeuroNEXT   RHAPSODY: A Multicenter, Phase II Study of 3K3A-APC with tPA in Ischemic Stroke

Currently, the only approved treatment in the U.S. for ischemic stroke is a drug called recombinant tissue plasminogen activator (rtPA or tPA), indicated for intravenous administration within three hours of onset of the stroke. The drug is designed to break down blood clots to restore blood flow to the brain. In some patients, however, tPA can cause internal bleeding and other complications. This multicenter, Phase II study uses a continual reassessment method to determine the safety, tolerability, and activity of 3K3A-APC, a recombinant variant of human activated protein C, in combination with tissue plasminogen activator, in subjects with moderately severe acute hemorrhagic ischemic stroke. The cytoprotective properties of 3K3A-APC may be useful in protecting ischemic brain tissue from further damage, while avoiding an increase in the chance of treatment-related bleeding.

The study intervention will be administered as a 15-minute infusion every 12 hours for up to 5 infusions. Four dose levels will be considered for this trial. Approximately 100 participants, ages 18 to 80 years old, will be enrolled and followed for 90 days.

For More Information
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NewYork-Presbyterian Awarded Advanced Certification as Comprehensive Stroke Center

NewYork-Presbyterian Hospital has been certified by The Joint Commission and the American Heart Association/American Stroke Association as a Comprehensive Stroke Center, the highest level of stroke certification a hospital can receive. The Hospital joins the elite group of certified Comprehensive Stroke Centers throughout the United States.

“Achieving advanced certification as a Comprehensive Stroke Center is incredibly important for us. We are extremely pleased to have been awarded this distinction,” says Steven J. Corwin, MD, President and CEO of NewYork-Presbyterian. “This award recognizes the extraordinary advances, research, and standard of care that NewYork-Presbyterian, Weill Cornell Medicine, and Columbia University Medical Center provide every day for New Yorkers.”

The Joint Commission’s Gold Seal of Approval® is awarded to institutions that provide the most advanced stroke care to patients with exceptional, around-the-clock treatment. According to The Joint Commission, a Comprehensive Stroke Center must meet all the general eligibility requirements for Disease-Specific Care and Primary Stroke Center certification. In addition, Comprehensive Stroke Centers are required to:

- Have dedicated neuro-intensive care unit beds for complex stroke patients and provide neuro-critical care 24 hours a day, seven days a week
- Have advanced imaging capabilities
- Maintain 24/7 availability of neurosurgeons, neurologists, neurointerventionalists, and neuroradiologists
- Meet minimum volume requirements for treating patients with a diagnosis of subarachnoid hemorrhage, performing endovascular coiling or surgical clipping procedures for aneurysms, and administering IV tPA
- Coordinate post-hospital care for patients
- Use a peer review process to evaluate and monitor the care provided to patients with ischemic or hemorrhagic stroke
- Participate in stroke research

The Joint Commission places industry-recognized standards on the clinical practice guidelines and requirements needed for accreditation. These requirements were developed in collaboration with the American Heart Association/American Stroke Association. To receive advanced certification, NewYork-Presbyterian underwent a rigorous screening process in April 2016 and received official certification on June 3.

“Stroke is the fifth-leading cause of death in this country,” says Dr. Corwin. “It is our responsibility as a leading Comprehensive Stroke Center to treat strokes accurately and effectively in order to save lives and combat the full range of neurological disorders.”
The overall goal of Dr. Gauthier’s imaging program is to combine all the imaging tools to study the MS lesion. “We are combining our PET, QSM, and myelin mapping to fully explore the extent of myelin damage developing as a result of multiple pathological events occurring within the early stage MS lesion. Nobody else is doing this. We have the expertise here to merge all the modalities together to really scrutinize the lesion.”

Dr. Gauthier and Dr. Vartanian are working with animal models to validate certain imaging tools that are key to their studies in MS. “Our work intersects,” says Dr. Gauthier. “Dr. Vartanian is very interested in what causes the lesion to occur and in identifying potential targets for remyelination. I take over with my imaging after the lesion has developed. Dr. Vartanian has a method to identify potential FDA-approved drugs that stimulate myelin repair in MS patients, and my imaging will help to translate his laboratory results to a clinical study for myelin repair.

“We’re very good at controlling the inflammation, so when we look at conventional MRI and count lesions, that’s fine for our medications that decrease new lesions,” continues Dr. Gauthier. “But we want to repair. There are only a few imaging researchers around the world who are utilizing imaging to understand myelin damage in MS; at Weill Cornell, we feel that this is an essential area to explore given that remyelination may prevent nerve loss and progressive disability. I do believe we’ll have some exciting results from this work. We’re at the development phase, where we are asking the questions. It’s an exciting time in the field, especially with repair and remyelination. We’re really at the forefront with our imaging modalities to study and gain more information.”