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Risk of Stroke and Carotid Plaque Thickness Elevated by Infectious Burden

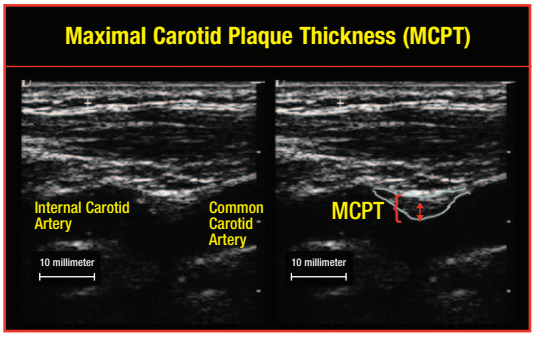
Contributing faculty for this article: **Mitchell S.V. Elkind, MD, MPH**

Cumulative exposure to a variety of common pathogens may increase an individual's risk of atherosclerosis and stroke, according to two new studies by investigators at NewYork-Presbyterian Hospital/Columbia University Medical Center. If the findings can be confirmed in additional studies, they could lead to the development of another tool for physicians to estimate an individual's risk of stroke. The studies were published in the January 2010 issue of the *Archives of Neurology* and the March 2010 issue of *Stroke*.

"There may be an association between infection, inflammation, and risk of vascular disease," explained Mitchell S.V. Elkind, MD, MPH, Associate Professor of Neurology at Columbia Universtiy College of Physicians and Surgeons and lead author of the studies. "Chronic, low-grade infections may contribute to vascular injury, but may not be the sole cause. More research is necessary to clarify the nature of these associations."

While smoking, hypertension, and cholesterol have been implicated in stroke, cerebrovascular disease also occurs in patients without any of these factors. Prior studies have provided evidence of an association between certain bacteria and viruses with atherosclerosis, coronary artery disease, and stroke. For example, investigators have shown that the aggregate burden of chronic infections, rather than any single pathogen,

see Risk of Stroke, page 2



Maximal carotid plaque thickness, a non-invasive measure of carotid atherosclerosis, is measured using high-resolution Doppler ultrasound in participants of the Northern Manhattan Study. The green line outlines the carotid plaque, which can then be measured on the computer screen.

NewYork-Presbyterian Pioneers Delivery of Intra-arterial Bevacizumab Into Glioblastoma

Contributing faculty for this article: **John A. Boockvar, MD, and Howard Riina, MD**

Neurosurgeons at NewYork-Presbyterian Hospital/Weill Cornell Medical Center have become the first in the world to perform intra-arterial cerebral infusion of bevacizumab (Avastin®) directly into glioblastoma multiforme (GBM) tumors in patients. This approach may enable physicians to treat GBM with higher, potentially more effective doses of bevacizumab while sparing patients from the adverse side effects associated with systemic use of the drug.

"By infusing bevacizumab directly into a tumor via the cerebral arteries, we may be able to kill cancer cells hiding within the tumor as well as in adjacent brain tissue. This new technique may be a way to get through the blood-brain barrier to deliver higher doses of the drug to the tumor with less toxicity to the patient," explained co-author and study co-principal investigator (PI) John A. Boockvar, MD, Director of the Brain Tumor Research Laboratory at NewYork-Presbyterian/Weill Cornell.

Bevacizumab was approved in May 2009 by the U.S. Food and Drug Administration for the intravenous treatment of GBM. But the treatment of brain tumors has been hampered by the inability of many intravenously administered anticancer drugs to permeate the blood-brain barrier.

In the past, the investigational administration of cisplatin via the carotid artery in patients with GBM resulted in serious side effects such as blindness and seizures, and did not demonstrate anticancer efficacy.

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may contribute to atherosclerosis and elevate the risk of clinical vascular events, including ischemic stroke.

This aggregate burden of infections, termed "infectious burden," may be linked to stroke through mechanisms that are independent of atherosclerosis, such as platelet aggregation and endothelial dysfunction. In addition, host factors may interact with infectious burden to alter the risk of disease associated with these infections.

Previous studies exploring these relationships have given these pathogens equal weight when assessing their influence on stroke risk. Dr. Elkind and his colleagues were the first to develop a quantitative index of infectious burden by weighting and summarizing an individual's history of infection with five common bacteria and viruses: *Chlamydia pneumoniae, Helicobacter pylori,* cytomegalovirus, herpes simplex virus 1, and herpes simplex virus 2. In a prospective investigation called the Northern Manhattan Study, the investigators followed 1,625 subjects for 8 years to assess the link between these pathogens and stroke risk.

Participants were enrolled between 1993 and 2001 if they had no prior diagnosis of stroke, were over age 39, and resided in northern Manhattan in New York City. While the researchers found an elevated risk of stroke associated with each individual pathogen, none of the associations achieved statistical significance. However, subjects' infectious burden was found to increase the risk of stroke, even after controlling for potential confounding variables, such as demographics, risk factors, and inflammatory biomarkers, such as high-sensitivity C-reactive protein. The risk increased by 39 percent for each standard deviation increase in the infectious burden measure. The link between infectious burden and stroke was especially pronounced among diabetic patients, whose risk was elevated by 63 percent (compared with just 29 percent among nondiabetic individuals).

This aggregate burden of infections, termed "infectious burden," may be linked to stroke through mechanisms that are independent of atherosclerosis, such as platelet aggregation and endothelial dysfunction.

The second analysis examined the relationship between carotid plaque thickness among 861 individuals from the Northern Manhattan Study, 52 percent of whom turned out to have carotid plaque. When adjusted for demographic and risk factors, history of infection with cytomegalovirus (but none of the other four pathogens) was positively associated with maximum carotid plaque thickness.

Infectious burden was also associated with carotid plaque thickness (increase in maximum carotid plaque thickness 0.09 mm per standard deviation increase of infectious burden), even after controlling for other variables.

Dr. Elkind cautioned that it is too soon to determine how these results will influence clinical practice. Some studies have assessed the long-term use of antibiotics to reduce risk, but these drugs were found to be of no value for this purpose. Dr. Elkind noted that long-term use of antibiotics may engender resistance to the drugs. Moreover, some pathogens, such as *C. pneumoniae,* may remain dormant in white blood cells, and in this inactivated state would not be susceptible to the lethal effects of antibiotics.

The Northern Manhattan Study is continuing to further elucidate the correlations between infectious burden, inflammation, atherosclerosis, and stroke. Many of the study participants are from low-income areas, making the data valuable for exploring the effects of socioeconomic factors on stroke risk.

Dr. Elkind is collaborating with investigators at Columbia University College of Dental Medicine to study the effects of periodontal infection on stroke risk. He is also analyzing the correlations between pathogens and stenosis in pediatric patients with stroke.

"Atherosclerosis is a complex disease. No single organism is likely to account for it," concluded Dr. Elkind. "Instead, if infection plays a role at all, it is probably in a more cumulative and continuous fashion."

Pilocytic Astrocytomas in Adults More Likely to Become Malignant

Contributing faculty for this article: **Michael B. Sisti, MD, and Jeffrey N. Bruce, MD**

Pilocytic astrocytoma is the most commonly seen glioma in children, accounting for some 20 percent of intracranial pediatric tumors. They are generally benign and curable with surgical resection. But a study by investigators at NewYork-Presbyterian Hospital/ Columbia University Medical Center has reported that when pilocytic astrocytoma occurs in adults, the outcome may not be as favorable, with tumors being more likely to recur and become malignant. The study was published in the December 2009 issue of the *Journal of Neurooncology*.

"The diagnosis of pilocytic astrocytoma has a different meaning in adults than it does in children," said Michael B. Sisti, MD, James G. McMurtry Associate Professor of Clinical Neurosurgery, Radiation Oncology and Otolaryngology at Columbia Universtiy College of Physicians and Surgeons and senior author of the study. "It may carry a more ominous prognosis in adult patients than in pediatric patients. Our findings demonstrate how little we know about how tumors behave in different age groups." The World Health Organization classifies pilocytic astrocytoma as a grade I astrocytic tumor. They represent 5 to 6 percent of all gliomas. Pilocytic astrocytomas are usually slow-growing and well-circumscribed and amenable to surgery. Yet studies of this tumor in adults have produced conflicting results, with some showing that the tumors follow a benign clinical course after surgical resection and others reporting that tumor recurrence and malignant transformation occur relatively frequently.

"While pilocytic astrocytomas in adults are quite rare, they may be more dangerous than we thought. You can't let your guard down with these tumors."

— Jeffrey N. Bruce, MD

see Pilocytic Astrocytomas, page 7

Tapering Off Dopamine Agonists in Parkinson's Disease Can Trigger Withdrawal Syndrome

Contributing faculty for this article: **Melissa J. Nirenberg, MD, PhD**

Researchers at Weill Cornell Medical College have identified for the first time "dopamine agonist withdrawal syndrome (DAWS)," which occurs in some patients who reduce their dosage of or stop taking dopamine agonists (DAs) for Parkinson's disease (PD). Patients who experience DAWS report symptoms similar to those of cocaine withdrawal, which are highly distressing and disruptive to their quality of life, and not alleviated by other PD medications. The findings were published in the January 12, 2010 issue of the *Archives of Neurology.*

"Like cocaine and amphetamines, dopamine agonists work by stimulating reward pathways in the brain," said Melissa J. Nirenberg, MD, PhD, Associate Director of the Parkinson's Disease and Movement Disorders Institute at NewYork-Presbyterian/Weill Cornell and Assistant Professor of Neurology and Neuroscience at Weill Cornell Medical College, who led the study. "For this reason, it makes sense that these drugs would engender similar withdrawal symptoms."

DAs are used in some PD patients instead of, or in combination with, L-DOPA. Two DAs are currently on the market in the United States: pramipexole (Mirapex®) and ropinirole (Requip®, Requip XL®). These medications are also FDA approved for use in restless legs syndrome (RLS), and sometimes used off-label to treat other conditions such as depression and fibromyalgia.

DAWS symptoms include anxiety, panic attacks, depression, sweating, nausea, generalized pain, fatigue, dizziness, and drug cravings. DAWS only occurred in patients who experienced DA-related impulse control disorders (ICDs) such as compulsive eating, gambling, shopping, and hypersexuality. ICDs are a known side-effect of DAs, occurring in about 14 to 17 percent of PD patients who use these drugs. "Right now, the only known way to treat ICDs is to reduce the dosage of the dopamine agonist or discontinue these medications altogether," Dr. Nirenberg commented.

Dr. Nirenberg advises physicians who prescribe DAs to educate their patients about the possible side effects associated with these medications and their withdrawal. She interviews her own patients extensively about their habits and behaviors before and throughout DA treatment. "ICDs can be severe, and are underreported. Patients may not discuss ICDs with their physicians because they are embarrassed, in denial, or unaware that their symptoms are caused by PD medications," added Dr. Nirenberg.

Dr. Nirenberg and first author Christina A. Rabinak, a third-year medical student at Weill Cornell Medical College, performed a retrospective cohort study of 93 people with PD. Forty of them received pramipexole, and 26 tapered from the drug for a variety of reasons — most commonly because of ICDs. Among those who tapered pramipexole, five patients (19 percent) experienced DAWS, all of whom had a history of ICDs.

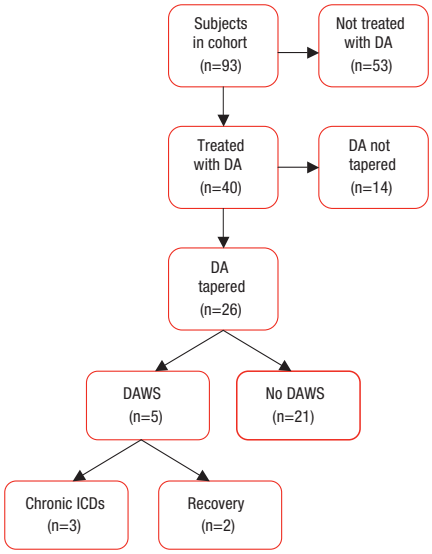
DAWS correlated with higher baseline DA use and higher cumulative DA exposure. "This suggests that tapering DAs as soon as ICDs occur may reduce the risk of DAWS," said Dr. Nirenberg.

In the study, the symptoms of DAWS were refractory to L-DOPA, other PD medications, antidepressants, benzodiazepines, and psychotherapy, and only responded to restarting or increasing the dose of the DA. Two of the subjects with DAWS eventually recovered fully, but three of the five were unable to successfully discontinue DA treatment because of severe withdrawal symptoms. These three study participants are currently living with disabling ICDs. "Until researchers identify alternative treatments for ICDs or DAWS," said Dr. Nirenberg, "I recommend that physicians and their patients use DAs judiciously, taper them as soon as ICDs develop, and exercise caution when they are tapered."

Dr. Nirenberg noted that patients taking DAs for other indications, such as RLS, might potentially also be at risk of DAWS. She is collaborating with investigators in NewYork-Presbyterian/Weill Cornell's Center for Sleep Medicine to monitor for possible DAWS symptoms in RLS patients who taper a DA.

She is also studying the neural pathways that mediate reward and impulse control to identify predictors of DAWS, a collaboration with NewYork-Presbyterian/Columbia researchers Rachel Marsh, PhD, and Bradley S. Peterson, MD. They are using functional MRI to analyze patterns of brain activation in PD and correlate the results with DA use and the presence of ICDs. "ICDs are also a novel, reversible human model for addiction, in which patients can be evaluated before, during, and after the addiction develops," Dr. Nirenberg explained. "Studying ICDs and DAWS may therefore help to elucidate the biological basis for addiction disorders."

Chart 1: Flowchart showing DA treatment and outcomes in the cohort



Key: DA = dopamine agonist DAWS = dopamine agonist withdrawal syndrome

Chart 2: Baseline demographic and clinical features of DAWS subjects

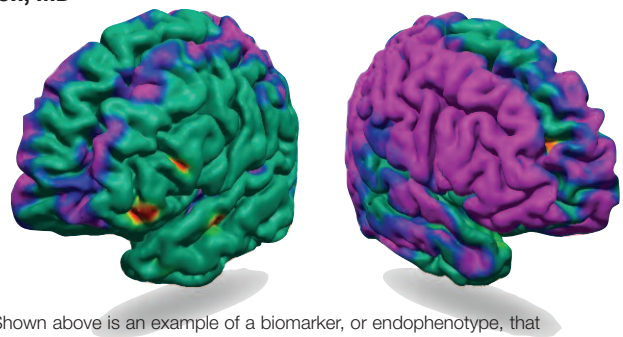
Subject	Sex	Age	Age of PD Onset	Impulse Control Disorder(s)
A	F	67	60	Hypersexuality, buying, eating, sorting pills
B	F	61	55	Eating, buying, cleaning, painting, organizing
C	F	64	45	Eating, sorting pills
D	M	69	65	Hypersexuality
E	M	57	57	Hypersexuality, shopping, eating, gambling, praying

Key: DAWS = dopamine agonist withdrawal syndrome F = Female M = Male

Clinical and Scientific Authorities Seek to Explain Autism

Contributing faculty for this article: **Barry Kosofsky, MD, PhD, and Bradley Peterson, MD**

Researchers at NewYork-Presbyterian Hospital are galvanizing expertise from clinicians and scientists on both campuses to shed light on autism. Does it begin in the DNA? Do environmental factors play a role? Are there biomarkers and biological subtypes of autism spectrum disorders? These are a few of the questions that researchers are exploring in the new Weill Cornell Autism Research Program sponsored by the Clinical and Translational Science Center of Weill Cornell Medical College, and through the Division of Child and Adolescent Psychiatry of Columbia University Medical Center and the New York State Psychiatric Institute.



Shown above is an example of a biomarker, or endophenotype, that Bradley Peterson, MD, his colleague Myrna Weissman, MD, and others have detected in persons who are at an increased familial risk for developing Major Depressive Disorder. The marker consists of thinning of the cortex of the right cerebral hemisphere (purple in the above views, in which the right hemisphere is positioned on the right side of the figure and the left hemisphere is position on the left side of the figure).

The Role of Genetic Factors

"There is tremendous interest as to whether there is an epidemic of autism and why. Is it genetic? Is it environmental? Is it caused by immunizations? To better understand the potential causes, we first have to get a handle on the various types of autism that exist," noted Barry Kosofsky, MD, PhD, Chief of Pediatric Neurology in the Phyllis and David Komansky Center for Children's Health at NewYork-Presbyterian/Weill Cornell. "The Weill Cornell Autism Research Program (WCARP) has both a clinical and a basic science component, including an IRB-approved investigational study, to help us improve our understanding of the genetic and biochemical basis for autism." Dr. Kosofsky, who has assembled a multidisciplinary team of investigators to pursue this new research program, is the Horace W. Goldsmith Foundation Professor of Pediatrics, and Professor of Neurology and Neuroscience at Weill Cornell Medical College. His basic research team has developed animal models of disease that affect human brain development, including mouse models of autism.

The clinical diagnosis of autism spectrum disorders includes Asperger's disease, autism, pervasive developmental disorder, and other genetic syndromes that cause autistic-like features, such as tuberous sclerosis and fragile X syndrome. "If we can better identify the physical or behavioral features patients demonstrate," said Dr. Kosofsky, "we would have a starting point for looking at contributing genetic factors to autism and, potentially, associated imaging changes."

To accomplish this, the WCARP team has embarked on a genetic study of intellectual disabilities and autism spectrum disorders to identify factors linked to these conditions. Every Wednesday morning, the team meets to evaluate individuals with autism enrolled in the study, as well as their parents and siblings. The comprehensive assessment involves a detailed clinical evaluation, including neuropsychological testing and blood tests, carried out by scientists and clinicians from the Departments of Pediatrics, Neurology, Developmental Pediatrics, Psychiatry, and Medicine.

"There are three axes to our analysis," says Dr. Kosofsky. "One is the clinical phenotype – what does a particular patient with autism look like when assessed by a child neurologist, a developmental pediatrician, and a child psychologist." Leading the neuropsychological assessments section of the study are Mary Jo Ward, PhD, Associate Research Professor of Psychology in Pediatrics and Psychiatry, and Emily Forrest, MD, an Instructor in Pediatrics in the Division of Child Development. Drs.Ward and Forrest are using standardized instruments, including the research-based Autism Diagnostic Observation Schedule (ADOS), to aid in the diagnosis of autism and other pervasive developmental disorders, and the Vineland Adaptive Behavior Scale, to measure personal and social skills needed for everyday living. This testing will enable researchers to identify individuals who have intellectual and developmental disabilities, developmental delays, autism spectrum disorders, or other impairments.

Kaleb H. Yohay, MD, an Assistant Professor of Pediatrics and Child Neurology at Weill Cornell Medical College and Director of the Neurofibromatosis Clinic at NewYork-Presbyterian/Weill Cornell, serves as Clinical Director of the WCARP Study. Dr. Yohay assesses study participants for features of tuberous sclerosis and fragile X to exclude these and other genetic syndromes known to cause autism. "If he excludes other known mono-genetic causes of autism, and he and the research team reach a consensus diagnosis that the child has autism, we then draw blood for testing in a number of different research areas," explained Dr. Kosofsky.

Among these is the laboratory of Barbara Hempstead, MD, the O. Wayne Isom Professor of Medicine and Co-Chief of the Division of Hematology and Medical Oncology. With grant funding from Autism Speaks, Dr. Hempstead studies levels of a neurotransmitter called brain derived neurotrophic factor (BDNF) in patients with autism. Armin Alaedini, PhD, Assistant Professor of Neuroscience, is interested in autoimmune issues that relate to gastrointestinal disease observed in a subset of those with autism, work being funded by the Department of Defense. In addition, the study group collaborates with Eli Hatchwell, MD, PhD, Director of the Genomics Core Facility and Associate Professor of Pathology at Stony Brook University Medical Center, who has been conducting sophisticated genetic testing on a panel of genes identified as causing autism. Dr. Hatchwell is screening WCARP patients and their family members for rare but known genetic defects, as well as some that may be unknown.

Investigators Joseph J. Higgins, MD, Professor of Pediatric Neurology, and Anjali M. Rajadhyaksha, PhD, Assistant Professor of Neurology in Pediatrics and Assistant Professor of Neuroscience, Weill Cornell Medical College, are studying the role of calcium signaling and its contribution to autistic features. see **Autism,** page 5

continued from **Autism,** page 4

These investigators have been funded by the March of Dimes and the Hartwell Foundation, respectively, to develop and study lines of transgenic mice with defects in calcium signaling, which, in a subset of patients, have been associated with autism spectrum disorders (ASD). Dr. Higgins, a neuro-geneticist who has long been involved in the genetics of mental retardation and autistic spectrum disorders, serves as the Principal Investigator of the over-arching Clinical and Translational Sciences Center study, which integrates each of these independent lines of research. Dr. Jeff Fisher, Clinical Professor of Medicine at Weill Cornell Medical College, has played an instrumental role in galvanizing interest and support for the WCARP.

Dr. Kosofsky's piece of the puzzle is in brain imaging. "We are interested in identifying individuals whose brains grow too big and too fast, which has been seen in some autistic children, and to see whether that might be a marker of disease in these children." Although autistics may look similar from the outside, they may not be on the inside. Looking at genetic information as well as structural brain information, the researchers may be able to break out subtypes of autism, which may have implications for potential therapies.

"This is strictly a research-based study in which we are correlating clinical manifestations of ASD with patterns of genetic abnormalities in calcium signaling and regulation, and alterations in BDNF levels in blood platelets – all of which have been implicated in the pathogenesis of ASD," said Dr. Kosofsky.

Identifying Brain-Based Biomarkers

Bradley Peterson, MD, Chief of the Division of Child and Adolescent Psychiatry at Columbia University and the New York State Psychiatric Institute and Director of Pediatric Neuropsychiatry, has a special interest and decades of research expertise in MRI and its role in identifying abnormalities in the brains of children and adults who have serious neuropsychiatric disorders.

"It has become increasingly clear that many of the findings that have been reported both in our laboratories and in all other laboratories across the country likely aren't representing the causes of disorders as much as the consequences of having a disorder," said Dr. Peterson. "Often people who have chronic neuropsychiatric problems have a high level of stress and environmental disruption that can effect their brain structure and function, or they are undergoing medication or behavioral therapies, which are also having powerful effects. Disentangling the causes of an illness from its consequences has been very, very difficult in human biological research.

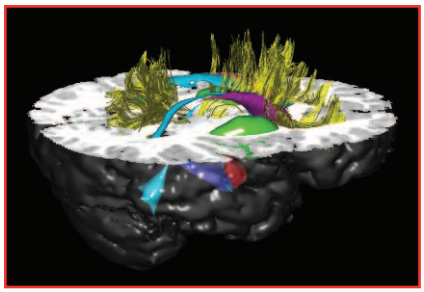
"A major problem is that these are naturalistic studies," Dr. Peterson continued. "We can't randomize people to have an illness or not. And, frequently, the reasons people come for clinical care or for imaging studies have to do with the disorder's effects, such as stress, poor functioning, or co-morbid illnesses, or a failure to respond to treatments. When you compare those people against healthy community controls who don't have the illness, there are a number of issues that can be responsible for the abnormality having nothing to do with the cause of the disorder."

One way to help sort out these issues is to study subjects who have a high familial risk for developing an illness. A general strategy that Dr. Peterson and his colleagues are applying to the study of autism is to identify brain abnormalities or endophenotypes that predispose a person to becoming ill. "These are enduring traits in the brain, which along with the illness, should be heritable," noted Dr. Peterson. "These endophenotypes should be present across the life span – early in life, as well as late in life," said Dr. Peterson. "Therefore, we have been studying both children and adults who have this illness. The factors we find in common in both children and adults, as well as in unaffected family members, are very likely to represent causes of the illness rather than the consequences."

In September 2009, Dr. Peterson and his colleagues began a study using multimodal magnetic resonance imaging – anatomical MRI, functional MRI, diffusion tensor imaging, and magnetic resonance spectroscopy – to identify brain-based biomarkers and biological subtypes in individuals with an ASD and measure brain chemical and metabolite concentration. Obtaining multiple imaging modalities from the same cohort is invaluable because the findings from one modality help to constrain interpretations of findings from another.

The project complements and leverages MRI data currently being collected under the auspices of a National Institutes of Mental Health American Recovery and Reinvestment Act stimulus grant in 100 children and adults with ASD and 100 age- and sex-matched healthy comparison subjects.

According to Dr. Peterson, this will enable them to identify the same brain-based disturbances in structure and function as are present in the ASD cohort, ensuring that the abnormality truly represents a brain-based vulnerability for ASD, rather than simply being a consequence of having the chronic disabling disorder, representing a compensatory response to having an ASD, or of being an effect of medication or other treatment.



Shown here is the brain viewed from the right side in which the upper half has been removed to show bundles of nerve fibers (yellow) mapped using Diffusion Tensor Imaging, subcortical brain regions (purple and green), and the lateral ventricles (blue). (Image compliments of Dr. Peterson)

Dr. Peterson has already collected quite a bit of data of anatomical brain abnormalities in those with autism versus healthy controls. "In a preliminary review, we have seen very prominent abnormalities," noted Dr. Peterson. "These abnormalities, which appear to involve lateral aspects of the brain that surround the Sylvian fissure, are located in the temporal lobe, inferior parietal lobe, and the inferior frontal lobe. These areas are very important in the processing of language, which is a key tool for social communication, and social communication is one of the fundamental disturbances in autistic people. We haven't yet determined whether the degree of this disturbance or the magnitude of the abnormality relates to clinical severity. These same brain regions and circuits are also near mirror neuron circuits within the brain that have to do with understanding the intentions of movements of another person. This, too, is thought to be a key prerequisite capacity for people to develop social awareness."

Identifying biomarkers and biological subtypes of this heterogeneous condition will benefit the search for vulnerability genes for ASD, as well as enable future strategies for prevention, early detection, and personalized treatment of these conditions. A full set of analyses is expected by the summer of 2011.

Eating Disorders Focus of New Inpatient Program

An eating disorder is marked by a disturbance in eating behavior together with psychological distress or impairment. This could include extreme food restriction, overeating or abnormal compensatory behaviors following food ingestion together with significant distress or concern about body weight or shape. Anorexia nervosa and bulimia nervosa are the most common of these conditions, which in severe cases can be life-threatening. In fact, it has been reported that anorexia nervosa has a mortality rate as high as that seen in any psychiatric illness.

In December 2009, NewYork-Presbyterian Hospital, Weill Cornell Medical College, and Columbia University College of Physicians and Surgeons, in affiliation with the New York State Psychiatric Institute, announced the creation of an integrated eating disorders center under the direction of Evelyn Attia, MD. Dr. Attia currently serves as Director of the Columbia Center for Eating Disorders at the New York State Psychiatric Institute and Clinical Professor of Psychiatry at Columbia University College of Physicians and Surgeons. A prominent researcher in the psychobiology and treatment of anorexia and other eating disorders, Dr. Attia was also named Professor of Clinical Psychiatry at Weill Cornell Medical College.

The Outlook at NewYork-Presbyterian Hospital/Westchester Division in White Plains – a key clinical component of the new center – is the only specialized psychiatric inpatient eating disorders program in New York State. The Outlook provides treatment for adolescents and adults with anorexia nervosa, bulimia nervosa, as well as binge eating and other eating-related disorders. The spacious unit has 17 beds – six for adolescents and 11 for adult patients. The program's multidisciplinary team includes two full-time psychiatrists, psychologists, social workers, nursing staff, nutritionists and therapeutic activities staff.

"For individuals with acute eating disorders, hospitalization is the best way to address what can often be life-threatening medical and psychiatric complications," says Dr. Attia. "The Outlook offers patients and their families a level of care unavailable in a general psychiatric unit."

Dr. Attia is also the Program Director for one of three New York State–designated Comprehensive Care Centers for Eating Disorders – a joint program of NewYork-Presbyterian Hospital, the New York State Psychiatric Institute, and Schneider Children's Hospital in Long Island. She has received continuous funding from the NIH for her work since joining Columbia's Eating Disorders Research Unit in 1999, as well as grants from private foundations and industry. She is the author of numerous peer-reviewed publications and is currently a member of the DSM-V (Diagnostic and Statistical Manual of Mental Disorders) Eating Disorders Workgroup. Among her many awards, she has received a Mentored Patient-Oriented Research Career Development Award from the National Institute for Mental Health for her study titled *Serotonin's Role in the Psychobiology of Anorexia Nervosa.*

"One of our leading authorities on eating disorders, Dr. Attia has been a major force for improving care for patients with these challenging conditions. She has been instrumental in understanding the biological basis of anorexia nervosa and in developing effective new treatments," says Jeffrey A. Lieberman, MD, Chairman of the Department of Psychiatry at Columbia University College of Physicians and Surgeons, Director of the New York State Psychiatric Institute, and Psychiatrist-in-Chief at NewYork-Presbyterian Hospital/Columbia University Medical Center.

"For individuals with acute eating disorders, hospitalization is the best way to address what can often be life-threatening medical and psychiatric complications."

— Evelyn Attia, MD

An estimated 5 to 7 percent of U.S. females will suffer from an eating disorder during their lifetimes and the disorder typically starts in adolescence, interrupting young lives at a critical developmental period when social pressures are more keenly felt. This can be a tremendous challenge for families. "This is exacerbated by the fact that for many, effective treatment is neither easily accessible nor inexpensive," noted Dr. Attia. "The Outlook, as its name implies, will allow patients to do the hard psychological work of shifting their views about their diagnosis and taking the necessary steps towards recovery."

Reflecting its park-like setting at NewYork-Presbyterian/Westchester, The Outlook's interior space is decorated with nature photography by artist Nadine Levin, whose images imbue the unit with a sense of calm.

"Eating disorders seriously imperil the health and well-being of those affected, while also presenting a major challenge for their families," says Jack Barchas, MD, the Barklie McKee Henry Professor and Chairman of the Department of Psychiatry at Weill Cornell Medical College, and Psychiatrist-in-Chief at NewYork-Presbyterian Hospital/Weill Cornell Medical Center and NewYork-Presbyterian Hospital/Westchester Division. "With the creation of this integrated eating disorders center, we bring together unprecedented clinical, research and educational expertise and resources so that we can better provide comprehensive and compassionate treatment that addresses each patient's specific needs in order to improve their health."

For more information about The Outlook or to make a referral, please call (888) 694-5700 or (914) 997-5700.

continued from **Pilocytic Astrocytomas,** page 2

In this study, which was led by resident physician Jason A. Ellis, MD, researchers retrospectively analyzed the clinical course of 20 adult patients at NewYork-Presbyterian/Columbia who had surgical resection of a pilocytic astrocytoma between 1995 and 2005. Six patients (30 percent) experienced a recurrence, including four whose tumors had been completely resected at surgery. Four of those six patients required repeat surgery due to symptomatic progression. Recurrences occurred relatively quickly, with the median time to recurrence being 16.5 months. All recurrences occurred within four years of initial surgery; patients requiring repeat surgery experienced a recurrence within 17 months of their initial surgery.

The estimated rates of freedom from recurrence (FFR) at 12 and 24 months after initial surgery were 94 ± 5 percent and 76 ± 10 percent, respectively. A high rate of malignant transformation was observed in the patients who had repeat surgery, with 75 percent (three out of four) of them progressing to anaplastic astrocytoma on pathological examination. These three patients had radiation therapy for their recurrence. A suggestion that malignant transformation is somehow correlated with radiation therapy needs to be validated in future studies, the investigators noted.

"While pilocytic astrocytomas in adults are quite rare, they may be more dangerous than we thought. You can't let your guard down with these tumors," added study co-author Jeffrey N. Bruce, MD, Director of the Bartoli Brain Tumor Research Laboratory, and Co-Director of the Brain Tumor Center at NewYork-Presbyterian/Columbia. The factors associated with recurrence and malignant transformation of pilocytic astrocytomas in adults are not yet known, and need to be studied in larger prospective studies.

Drs. Sisti and Bruce advise a clinical approach for adult patients with pilocytic astrocytoma that includes:

- refraining from telling them that their disease is definitely curable, since some patients may recur and experience malignant transformation
- following patients closely, including periodic MRI exams, especially during the first four years after diagnosis
- understanding that patients may require repeat surgery, chemotherapy, and/or radiation therapy if the tumor does recur

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Dr. Howard A. Riina (left), and Dr. John A. Boockvar are pioneering an exciting new approach using intra-arterial bevacizumab for the treatment of recurrent malignant brain tumors and have received approval for a full Phase II study.

The advent of targeted anticancer therapies, coupled with the refinement of microcatheter techniques that enable physicians to deliver the treatment directly to the tumor, led to the current advance. "This new approach enables us to effectively get to the doorstep of the tumor," said Dr. Boockvar.

In a procedure called "super selective intra-arterial cerebral infusion," the investigators directed a hair-thin microcatheter through the carotid artery and into the smaller cerebral arteries deep in the brain. Once at the tumor site, they injected mannitol to open the blood-brain barrier. During the five-minute window afforded by mannitol, they were able to inject bevacizumab directly into the GBM tumor.

"This revolutionary delivery technique could potentially be more effective than currently available treatments. Our goal is to see if we can find a way to eliminate intravenous chemotherapy altogether for these patients, giving them better quality of life," said co-author and co-PI, Howard Riina, MD, Co-Director of Interventional Neuroradiology and Associate Professor of Neurological Surgery, Neurology and Radiology at Weill Cornell Medical College. The authors believe that this technique may herald the birth of a new field of 'interventional neuro-oncology.'

In the initial Phase I/II study, 16 patients have received intra-arterial bevacizumab up to a dose of 10 mg/kg. No patients have experienced progression of their tumors, and some have achieved a complete response. Only one patient has died (from pneumonia, two months after the treatment). No adverse events associated with the treatment have been reported.

The investigators are still enrolling patients for the study to determine if the maximum tolerated dose can be increased to 15 m/kg (a dose approved for the intravenous treatment of other cancers). Eligible participants include patients age 18 and older with a documented diagnosis of relapsed GBM, anaplastic astrocytoma, or anaplastic mixed oligoastrocytoma. Patients may have had prior bevacizumab treatment, but no more than six cycles which were completed at least six weeks prior to study entry.

The researchers also received approval for a full Phase II study of up to 100 patients. In addition, patients to date have received only one dose; in future research, the investigators may evaluate the use of repeated dosing in patients who experience tumor progression.

For more information and to inquire about patient enrollment in these clinical trials, contact Dr. Boockvar at jab2029@nyp.org or Sherese Fralin, RN, at (212) 746-1996.