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On the cover: Studies of axons in multiple sclerosis brain samples (cube in photo) and experimental models using new methods such as 3-D electron microscopy indicate that mitochondria are normally stationed along axons (upper reconstruction in photo) but may aggregate in disease states (lower reconstruction), and this may promote axon destruction. Approaches to understanding axonal mitochondria are featured in the article on page 25.
Welcome to the 2012 – 2013 issue of Neuroscience Pathways from Cleveland Clinic’s Neurological Institute. We are pleased to share with you, our specialist colleagues across the nation, some of the most compelling research and clinical innovations for adult and pediatric patients from across our broad institute.

The imperative for value-driven healthcare is an ever-present factor influencing our Neurological Institute, as I imagine it is for your practice or organization as well. At its essence, value in healthcare means taking care of patients in the right way at the right time and in the right place. The aim is to optimize patient outcomes while rationalizing costs and ensuring that interventions and treatment settings are wholly appropriate for the level of care needed.

I am pleased that this value proposition manifests itself in a number of the contributions to this issue. Take, for example, the article from our Center for Neuroimaging (p. 17) reporting outcomes following adoption of our “hyperacute MRI protocol” for assessment of candidates for intra-arterial therapy for acute stroke. This protocol was designed to direct interventions solely to those patients who will benefit from them and not to those who will not or who may be harmed by them. In the first 14 months after its adoption, the protocol reduced by half the number of patients treated with intra-arterial therapy while outcomes for our overall population of acute stroke patients improved significantly. In other words, better outcomes were achieved with fewer resources and with less potential harm to patients.

Similarly, the contribution from the Cleveland Clinic at Home service within our Center for Home Care and Community Rehabilitation (p. 9) reports on how the acute care hospitalization rate for our home care patients has consistently remained far below the national average as reported by the federal government. We attribute this success to a diligent commitment to delivering the right care at the right time in the most appropriate care setting.

Other articles provide windows into how we are harnessing the value of information technology to provide care in a more rational way, such as with the major rollout of the Cleveland Clinic Concussion app for the iPad® 2 (p. 11), and to empower patients to better track their progress, as with the home-based GO!® To Sleep interactive online program from our Sleep Disorders Center (p. 32).

These contributions run alongside reports on the sorts of basic science discoveries that have been a more traditional currency of value in healthcare, such as the work emerging from our Department of Neurosciences on the role of axonal mitochondria in multiple sclerosis, as profiled in our cover story (p. 25). Such discoveries typically involve alignment of resources and priorities across two or more centers within the Neurological Institute, which testifies to the value of collaboration — a theme that surfaces repeatedly throughout these pages.

As these examples demonstrate, value in healthcare can take many forms, and we are eager to continue pursuing them all in Cleveland Clinic’s Neurological Institute. I hope you find the examples of that pursuit featured here enriching and stimulating. We invite your comments on what you see within, and we welcome opportunities for collaboration to advance neurological care for all our patients.

Sincerely,

Michael T. Modic, MD, FACR
Chairman, Cleveland Clinic Neurological Institute
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Advanced Neuroimaging in Bipolar Disorder: Identifying Markers to Enable Earlier Diagnosis, Better Intervention

By Amit Anand, MD

Much of the progress in our understanding of bipolar disorder over the past decade stems from advances in functional MRI and other technologies that enable ever more sophisticated examination of the functioning brain. These technologies increasingly reveal the brain to be a highly connected organ and demonstrate the central role played by abnormalities in brain connectivity — as opposed to merely abnormalities in distinct brain regions — in mood disorders. My research team has played a leading role in identifying the contributions of brain connectivity to depression and bipolar disorder, and I am eagerly building on this research in my new position at Cleveland Clinic by leveraging advanced imaging equipment and exceptional opportunities for multidisciplinary collaboration.

Corticolimbic Disconnections in Mood Disorders

My team’s brain imaging research has focused on examining the pathophysiology of major depression and all phases of bipolar disorder to evaluate the connectivity between brain regions that may be abnormal in these disorders. Our objective has been to identify robust and consistent brain imaging markers for use in diagnosis as well as in predicting and monitoring treatment response.

Our team was the first to report connectivity abnormalities between the brain’s mood-regulating cortical regions and its mood-generating limbic regions in unmedicated major depressive disorder¹ and, more recently, in unmedicated bipolar disorder.² These studies used the relatively new measure known as resting-state connectivity. We found that connectivity abnormalities are present in both bipolar disorder and unipolar depression.²

We recently confirmed our initial study in bipolar disorder with one of the largest investigations to date of medication-free patients with bipolar disorder.³ This study identified state- and trait-related activation and connectivity abnormalities in all phases of bipolar disorder (including euthymia) and more precisely defined imaging markers of these abnormalities.

Sorting Bipolar from Unipolar Depression in Young Adults

We are now building on those imaging findings in a new National Institutes of Health-supported study that I am beginning at Cleveland Clinic. Our study aims to identify brain imaging markers that can predict which teenagers and young adults who present with depression are likely to develop bipolar disorder. This is a significant clinical question, as bipolar disorder typically manifests solely as depression in its early stages. So when young patients present with depression, it is very difficult to assess whether it is unipolar or bipolar depression. The distinction is critical because treating bipolar depression with an antidepressant can potentially induce severe mania and lead to a worsening of the illness. Further, because the prognosis is much worse in bipolar than in unipolar depression, early identification of bipolar disorder is key to effective early intervention to avoid major impairments in relationships and work performance as patients advance into adulthood.

Additional Research Frontiers, New Resources to Leverage

In conjunction with our brain imaging studies, we are collecting genetic samples from our research participants in an effort to use imaging markers as an endophenotype. Our hope is to better elucidate the genetic basis of bipolar disorder, which has eluded researchers working solely with a behavioral diagnosis.

Similarly, our imaging studies are assessing the effects of various treatments, including lithium, antidepressants and atypical neuroleptics, on brain activation and connectivity in both bipolar disorder and unipolar depression (Figure). Our hope is that insights from these studies may guide development of future pharmacotherapies.

The progress of these investigations will be fueled by the neuroimaging equipment and facilities now at my disposal in Cleveland Clinic’s Neurological Institute, including a research-dedicated 7T scanner to be acquired in early 2013. These facilities are enhanced by the close involvement of the institute’s radiology specialists in clinical and research initiatives, the engagement of expert physicists in developing new imaging protocols, and the large base of patients with mood disorders in Cleveland Clinic’s urban setting.

As the new Vice Chairman for Research in the Center for Behavioral Health, I look forward to working with this large patient base and to tapping the Neurological Institute’s abundance of opportunities for interdisciplinary collaboration across the spectrum of behavioral health research. The lessons we learn about the centrality of brain connectivity in mood disorders will undoubtedly yield insights for neuropsychiatric disorders more broadly.
Dr. Anand is Vice Chairman for Research and Director of the Mood Disorders Clinical and Research Program in Cleveland Clinic’s Center for Behavioral Health and Department of Psychiatry and Psychology. His specialty interests include brain imaging, bipolar disorder, major depression and psychopharmacology. He can be contacted at 216.636.2840 or ananda@ccf.org.

REFERENCES


First-in-Kind Study Examines Brain Injuries in Boxers and Other Fighters

By Charles Bernick, MD

The tragic deaths of several well-known and relatively young athletes over the past few years have raised awareness of the potential long-term consequences of cumulative head trauma. Clinicopathologic studies have identified a neurodegenerative condition that is linked to repetitive head injury. This condition is known as chronic traumatic encephalopathy (CTE). The Cleveland Clinic Lou Ruvo Center for Brain Health is taking a leading role in this emerging field of study.

A Long-Recognized Association Remains Little Understood

The knowledge that head trauma can lead to progressive neurologic deterioration is not new, of course. This has been recognized since 1928, when New Jersey pathologist Harrison Martland described the clinical abnormalities seen in a substantial number of boxers. Over the subsequent decades, pathologic evidence of CTE has emerged in association with a variety of sports, as well as among returning combat veterans who were exposed to blast injuries. Most recently, the National Football League has embarked on a widely publicized effort to recognize and prevent concussions. Yet despite the attention that this issue has engendered, little is known about the natural history of, and risk factors for, CTE. One reason is that we lack a biomarker or clinical indicator that can predict whether a person with a history of head trauma is in danger of developing permanent brain damage or is already on a trajectory of cognitive decline.

When one combs the literature on CTE and the long-term consequences of head trauma, the limitations of previous work become apparent. Most studies examining boxers and other types of combatants are cross-sectional and/or retrospective, they are limited to single outcomes (either psychometric or imaging) or the researchers did not have access to newer investigative technology.

Time for a Comprehensive, Longitudinal Investigation

The Professional Fighters Brain Health Study (PFBHS) was launched by the Lou Ruvo Center in April 2011. Our investigative team has four aims:

• To examine the cumulative effects of repetitive concussive and subconcussive injuries to the brain in a group of professional fighters (i.e., boxers and practitioners of the mixed martial arts (MMA)) in real time
• To detect the earliest and most subtle signs of brain injury using available MRI techniques (Figure) and other clinical measures
• To determine which factors make an individual more likely to develop chronic neurologic disorders such as dementia and parkinsonism
• To identify those individuals who are progressing to long-term neurologic disease

The study is designed to evaluate these fighters on a yearly basis for at least four years. Each evaluation will consist of a brain MRI, computerized testing of cognitive function, speech sample analysis, genotyping, inventories of mood and impulsivity, demographic data, sports and medical history, and a neurologic examination.

Intriguing First-Year Findings

At the one-year mark, close to 180 fighters had been enrolled in the PFBHS. This population was about evenly split between boxers and MMA fighters. They had a wide range of ages (19 to 43 years) and professional experience.

Cross-sectional analysis has already yielded some intriguing findings:

• A greater number of fights is associated with a lower volume of the thalamus, but only after a threshold of 15 fights.
• A much higher threshold is required to demonstrate a relationship between the number of fights and lower performance measures, such as reduced speed in processing information.

The apparent indication that brain structural damage may precede performance decline is consistent with what we know about other neurodegenerative diseases, such as Alzheimer disease and Parkinson disease — specifically, that a significant amount of subclinical disease must occur before symptoms become apparent. Still, these findings need to be confirmed by longitudinal observation.
The number of fights was also related to other outcomes. For example, those subjects who fought more were more likely to have evaluation scores indicating less self-control. In addition, the number of fights and the number of times a fighter was knocked out were associated with alterations in MRI-based resting-state connectivity measures as well as fiber-tract integrity across the corpus callosum. The ongoing collection of longitudinal data is expected to confirm and extend these findings.

Some New Technologies as Well

The study’s output is expected to be enhanced by the application of new technologies that have been developed at Cleveland Clinic. A mobile iPad®-based test that can be used for the brief assessment of brain function has already undergone pilot testing during one fight card, and we plan to use it during sparring sessions. The aim is to understand the types of changes that can occur from repetitive subconcussive injuries, which many researchers believe may be most responsible for long-term brain injury. A complementary device is being developed that can be integrated into a mouthguard to measure impact forces to the head.

While the definitive means of protecting athletes from developing CTE would be to restrict blows to the head entirely, this is not realistic given the current structure of many contact sports. However, the compilation of more knowledge of the natural history, risk factors and biomarkers of CTE should assist regulatory agencies in developing objective guidelines and in advising athletes of their status in the hope of preventing long-term neurologic complications. Output from studies such as the PFBHS will help provide such information.

Dr. Bernick is Associate Medical Director of the Cleveland Clinic Lou Ruvo Center for Brain Health, Las Vegas. His specialty interests include Alzheimer disease, dementia and memory loss. He can be contacted at 702.483.6030 or bernicc@ccf.org.
Research into Molecular Motors Holds Hope of Halting Glioblastomas in Their Tracks

By Steven S. Rosenfeld, MD, PhD

New research from Cleveland Clinic’s Rose Ella Burkhardt Brain Tumor and Neuro-Oncology Center reveals that certain types of “molecular motors” enable cancerous glioblastoma cells to migrate and invade nearby tissue. It is this ability that explains why gliomas easily disperse throughout the brain, thereby limiting the effectiveness of treatments to date.

New Clues About How Gliomas Spread

Like the motor of a car engine, molecular motors cause malignant glial cells to physically move through the brain’s white matter and cortex. Intervening in or inhibiting the activity of these motors stops the cells from moving, opening the door to a new area of drug development for glioblastoma, which has a notoriously poor prognosis. The average survival time for a patient following a glioblastoma diagnosis is 12 months.

Glioblastomas represent a significant health burden, accounting for nearly half of all benign and cancerous CNS tumors. Malignant gliomas arise from abnormal glial cells — cells that support and protect neurons — and can easily infiltrate surrounding tissue, which makes it difficult to treat them effectively before they spread. Although the unique biology of gliomas poses a challenge for treatment, our research exploiting this biology is providing new clues about how gliomas spread.

As with most other cancer types, glioblastoma tumors are diverse in terms of their genetic foundation and the signaling pathways by which they grow, spread and circumvent attack by chemotherapy or radiation. This explains why there remains a pressing need to identify other targets of the glioma cells’ invasion apparatus.

Our research shows that at least four types of molecular motors appear to have a role in gliomas. All four are contained in the larger myosin family. Researchers in Cleveland Clinic’s Neurological Institute were the first to discover that molecular motors known as nonmuscle myosin (NMM) IIA and IIB are the essential motors behind glioblastoma invasiveness. The density of brain matter limits cellular navigation through narrow intercellular spaces. Yet glial cells overcome this limitation through NMM II contraction — fueled by the cells’ ATP energy supply — at the rear of the cancer cells, propelling them with the force needed to migrate (Figure).

A Focus for Drug Development

Our studies have shown that NMM IIA is found in high levels in gliomas but not in normal brain tissue, making it a potentially ideal focus for new drug development.

Diving deep into the science of these motors suggests that they contain a number of potential new targets for intervention that could block tumor dispersion and growth. We have identified at least two important compounds connected with NMM IIA and IIB — kinases known as ROCK and MLCK — that may prove fruitful targets for halting glioma cell invasion and spread.

Cleveland Clinic’s Neurological Institute is committed to developing new treatment strategies exploiting the molecular motor biology within glioblastomas. We are currently studying an existing drug — fasudil, which inhibits the activity of ROCK — in laboratory experiments and mouse models of glioblastoma. Our studies have shown that fasudil, which is currently used in Japan for treatment of pulmonary hypertension and post-stroke cerebral vasospasm, blocks cellular invasion in simple in vitro assays as well as in ex vivo brain-slice invasion assays. Further, fasudil reduces tumor spread in mouse models of glioblastoma. Other drugs with anti-NMM IIA and IIB activity are available as well and will be the focus of future glioma studies in the Neurological Institute.

Blocking invasion of glioblastomas will likely be just one part of treatment. Perhaps the most thorough approach will be one that inhibits tumor growth along with blocking NMM II-mediated invasion. To this end, our researchers are investigating therapies targeting NMM II in combination with existing treatments, such as radiation therapy, temozolomide chemotherapy or anti-angiogenesis drugs designed to kill glioma cells. The hope is to one day offer patients with glioblastoma a treatment strategy that will not only stop glioma cell development and growth but literally stop it in its tracks.

Dr. Rosenfeld is a neuro-oncologist with appointments in the Neurological Institute’s Rose Ella Burkhardt Brain Tumor and Neuro-Oncology Center and in the Lerner Research Institute’s Department of Cancer Biology. His specialty interests include neuro-oncology, brain tumors and brain tumor invasion. He can be contacted at 216.444.7984 or rosenfs@ccf.org.
Evolution in the Neurointensive Care Unit: Swifter Interventions with Quantitative EEG and 24/7 Specialist Coverage

By Stephen Hantus, MD, and Edward Manno, MD

Cleveland Clinic’s Neurointensive Care Unit (neuro ICU) is a specialized unit that receives the sickest patients from our 10 regional hospitals and has one of the highest patient acuity levels in the nation. Patients referred to our neuro ICU present with strokes, hemorrhages, tumors and other primary neurologic injuries that require constant monitoring. These patients are often unresponsive and have changes in cerebral blood flow, altered metabolism and seizures, often without any signs on clinical examination.

Responding to these changes is challenging and requires advanced monitoring and expert staff to act quickly on the information gathered. Neurophysiologic monitoring of these patients with continuous EEG (cEEG) has shown that 19 percent of this population is having seizures, often with no clinical signs. In addition, cEEG has been developed into a tool for measuring brain function in a variety of clinical circumstances that affect patients in the neuro ICU (Figure 1). Cleveland Clinic’s Cerebrovascular Center and Epilepsy Center have been working together to provide 24/7 coverage by epileptologists to interpret these studies and by neurointensivists to intervene with patient care. This article describes two innovations aimed at improving the care of the neuro ICU population: quantitative EEG monitoring and our model for 24/7 neuro ICU coverage by neurointensivists.

Benefits of Quantitative EEG in the Critical Care Setting

One of the major challenges of cEEG monitoring in the neuro ICU is managing a large quantity of data (Figure 2) in a time-efficient manner. A single 24-hour video EEG record comprises more than 8,000 screens of EEG, which require considerable time to review. The traditional model of EEG review is a single read every 24 hours. At the same time, outcome studies of nonconvulsive status epilepticus have demonstrated that delays in diagnosis and treatment lead to increased rates of disability and death, which argues for more frequent and/or more comprehensive monitoring.

Quantitative EEG is a graphical representation of EEG signals that allows for the display of multiple hours of data on a single screen and can be used to detect clinically useful patterns. The quantitative EEG is displayed in distinct spectral arrays that highlight a specific change to alert the reviewer to important regions of the record. One such variable displayed is the rhythmicity of the EEG (top of Figure 3), which identifies areas of the EEG that become more rhythmic (a characteristic of seizures as demonstrated in the figure). The power (amount) of each corresponding rhythm is displayed according to its frequency in the power spectrum, with seizures appearing like flames as a result of the increased array of frequencies seen (Figure 3). Seizures or ischemic events often occur in one hemisphere of the brain, and they are detected by comparing EEGs between one hemisphere and the other. Any asymmetries can be plotted in a spectral array, as shown in Figure 3, and can alert reviewers to seizures, cerebral vasospasms or other structural lesions. Amplitude-integrated EEG is also used to detect areas of concern in the EEG by plotting the maximum and minimum amplitudes of EEG, which often will identify areas of increased activity (Figure 3).

The combined use of these quantitative EEG trends allows for a prediction of seizure probability and automated seizure detection. As a result, quantitative EEG is enabling us to rapidly identify suspicious areas of the EEG that can provide focus to the EEG review and lead to a more swift and effective intervention.

Implementing Round-the-Clock Neurointensivist Coverage

The traditional academic model of ICU care delivery focused on morning rounds with the attending physicians, bedside nurses, pharmacists, residents and medical students. After rounds, procedures were completed, lectures given, notes written and patient management issues addressed. An abbreviated form of rounds was conducted as the daytime staff “signed out” to the nighttime
providers from either the ICU or the primary service. Resident physicians have been the historical nighttime providers and have been expected to recognize the onset of a crisis quickly and to notify the attending physician.

The most recent development in academic hospital care delivery has been increasing in-house coverage by attending physicians to a 24/7 basis. This model has largely been driven by work-hour reductions resulting from ACGME program restrictions. Several studies have evaluated the role of 24/7 attending physician coverage, primarily in medical ICUs. Some have evaluated the impact on morbidity and mortality by comparing night/weekend admissions with admissions during regular working hours. Most have reported that 24/7 attending physician coverage has had a favorable impact on mortality and length of stay. Many academic medical centers have subsequently moved to 24/7 attending physician coverage of their ICUs. Several employ a system in which one attending physician supervises several different ICUs that are individually staffed by residents, nurse practitioners or fellows. We believe this concept of cross-coverage has had a significant impact on the development of neurocritical care fellowship training programs.

Cleveland Clinic recently mandated that all its ICUs provide 24/7 attending physician coverage that is limited to the attending physician’s own subspecialty. We believe our neuro ICU is the only academic neuro ICU in the nation so far to require 24/7 coverage by an attending neurointensivist. Our policy of 24/7 attending physician ICU coverage has been met with enthusiasm by the nursing staff and most attending physicians from the various primary services. There are clear benefits in extending the completion of daytime workflow, as issues and delays can now be dealt with over the course of the evening. And there is also increased peace of mind for the daytime attending physician, who is now able to sign out to another senior neurointensivist colleague who will offer seamless continued management of the neuro ICU’s complex cases.

Dr. Hantus is a staff epileptologist in Cleveland Clinic’s Epilepsy Center as well as a staff physician in the Cerebrovascular Center and the Department of Neurology. His specialty interests include ICU monitoring in the critical care setting. He can be contacted at 216.445.9502 or hantuss@ccf.org.

Dr. Manno is Head of Cleveland Clinic’s Neurointensive Care Unit and a staff physician in the Cerebrovascular Center and Departments of Neurology and Neurosurgery. His specialty interests include neurocritical care quality measures and intracerebral hemorrhage. He can be contacted at 216.445.1624 or mannoe@ccf.org.
Cleveland Clinic at Home Drives Down Readmissions While Expanding Its Reach

By William Zafrana, MD, and Cindy Vunovich, RN, BSN, MSM

An increasing number of patients need home-based medical care. These include patients who require follow-up services after being hospitalized, are at the end of life, have complex diseases, or have comorbid conditions and limited mobility. Providing medical care and rehabilitation at home, rather than at a healthcare institution, is not only cost-effective but results in positive outcomes. Over the past few years, Cleveland Clinic at Home (CC at Home), through the Center for Home Care and Community Rehabilitation, has seen a dramatic reduction in hospital readmissions as well as other positive outcomes, including increased patient satisfaction. Nine CC at Home physicians are supported as faculty members within the Department of Physical Medicine and Rehabilitation, and 150 home care rehabilitation therapists benefit from close collaboration with Cleveland Clinic Rehabilitation and Sports Therapy, which operates systemwide.

Expanding Services, Increasing Access

Established in 1999, CC at Home is closely integrated with the Cleveland Clinic health system: All providers can access the same electronic medical record for patients, and all operations are in the same building, which facilitates communication and collaboration. Our mission is to provide care to patients who need it most but often have great difficulty accessing it. We offer a comprehensive, ever-expanding array of home-based services, as detailed in the sidebar. Patient education is an integral part of CC at Home: We teach patients and their caregivers the skills to provide ongoing care, which improves outcomes.

CC at Home served 18,000 patients in 2011 and currently sees 2,000 patients a month. Our reach is expanding as we have begun providing care remotely through telemedicine, which enables patients to transmit their vital signs — blood pressure, peak flows and blood sugar — to their primary care physician and specialists, and soon will allow them to have teleconferences with these providers.

Substantial Declines in Home Health Acute Hospitalizations

Between early 2008 and early 2011, acute care hospitalization rates for CC at Home patients declined from 29 percent to 18 percent, and they remained at that reduced level through late 2011 (Figure), according to publicly reported data from the Centers for Medicare and Medicaid Services (CMS). Our acute care hospitalization rate of 18 percent in late 2011 compared favorably with the national average of 27 percent for the same period (Figure). We attribute these outcomes to our responsiveness to patient needs: We visit patients soon after discharge, thoroughly review care plans with patients and caregivers, and respond quickly by phone and home visit when problems arise. Additionally, we work diligently to ensure that patients receive the right care at the right time across the continuum, which includes medical care at home, home health, palliative consultation and hospice at home. Working in concert with Cleveland Clinic’s Infusion Pharmacy at Home service, we provide complex infusions, nutrition support with total parenteral nutrition, and pain management in the home setting.

In 2011, CC at Home met or exceeded national benchmarks in 18 of 21 process-of-care, outcome and utilization outcome measures for rehabilitation care, according to publicly reported CMS data. Moreover, our patients appreciate receiving care at home: 86 percent gave CC at Home a satisfaction rating of 9 or 10 (out of 10), which compares favorably with the home care services of other leading medical centers.

Chosen for the CMS ‘Independence at Home’ Demonstration Project

Cleveland Clinic is one of 16 healthcare organizations nationwide selected to participate in the CMS demonstration project known as Independence at Home. CC at Home will work with CMS to test new models of healthcare delivery and measure the quality of care and patient outcomes. Independence at Home will expand and build on existing CC at Home services. If the project succeeds in improving quality measures while generating savings for the Medicare program, medical practices will receive incentive payments to further support and develop their home-based care programs.

Future Plans

In the coming years, as the senior population grows, we anticipate an increased need for home-based care and will expand CC at Home services to meet it.
Skilled nursing, our most commonly used service, provides physical assessments, medication monitoring and health instruction for patients and families.

Rehabilitation therapies offered in the home include physical and occupational therapy and speech-language pathology.

Respiratory Therapy at Home provides home oxygen, nebulizers and aerosol medications to patients with conditions such as obstructive sleep apnea, emphysema, chronic bronchitis, asthma and compromised heart function.

Heart Care at Home blends innovative telehealth monitoring technology with home healthcare services (when appropriate) to support patients following hospitalization for heart disease or heart surgery. This service also provides health coaching by registered nurses and home visits by advanced practice nurses for high-risk patients.

Infusion Pharmacy at Home is a licensed pharmacy service that provides medications, nutritional support, infusion pumps and comprehensive infusion therapy management. Therapies may be administered intravenously, subcutaneously or through an epidural line.

Hospice at Home assists patients and families in preparing physically, spiritually and emotionally for the end of life; it includes the Palliative Care Consultation Program to improve quality of life for patients with both incurable and advanced diseases. Our team of specially trained clinicians includes physicians, nurses, social workers and chaplains.

Medical Care at Home provides geriatric consults and primary medical care to patients with serious chronic conditions who have difficulty getting to a medical office, have memory disorders or behavioral health issues, or have been recently discharged from a medical facility. This is the newest and fastest-growing CC at Home service, currently serving 500 patients with chronic impairments.

Nutritional therapy offerings consist of comprehensive diet analysis and in-home nutrition assessments by registered dietitians.

Medical social services include comprehensive assessment of patients and families, education, support, counseling and referrals to community resources.

Additional specialty services include in-home diabetes management, wound care, and pre- and postnatal care.
Cleveland Clinic iPad App Takes the Guesswork Out of Concussion Assessment

By Jay L. Alberts, PhD, and Richard Figler, MD

The management of concussion in young athletes too often follows a scenario like this:

An athlete sustains a blow to the head in a Friday night game. He’s taken out of the game but “shakes it off” without going to the emergency room. He’s assessed for concussion by an on-site athletic trainer, but not in a well-documented way. What documentation there is rarely makes it to the electronic medical record. A few days later, the athlete’s mother is troubled that he’s “still not quite right,” so they go to a physician who must piece together conflicting recollections of what happened. The physician puts the athlete through a battery of tests three days after the injury. Without baseline data, it’s difficult to know the extent and focus of the patient’s impairment or how much recovery has taken place. Management is hampered by this uncertainty, and the patient’s family becomes dissatisfied, bouncing from one provider to another. Even worse, the athlete may be cleared prematurely because even though his functional test scores may look good, there is no way to know if he has fully returned to normal function.

Cleveland Clinic has a vision of how to change this model of sports concussion care, and we are extending the benefits of this vision to nearly 12,000 young athletes in Northeast Ohio. The vision centers on our proprietary concussion application (app) for Apple’s iPad® 2, a collaboration among our Concussion Center, Department of Biomedical Engineering and Center for Sports Health. We believe it can change the trajectory of concussion care by enabling objective, affordable, point-of-care assessment of the multiple symptoms associated with concussion and providing this information to clinicians in a meaningful manner on a device that allows for interaction with the data.

Why an iPad App?

When we began exploring a software-based model to monitor concussions, we knew that measurement of motion and acceleration would be key. When the iPad 2 came along, with a built-in gyroscope and accelerometer, it fit the bill.

The Cleveland Clinic Concussion (C3) app works by collecting position and time-series data, along with linear and angular acceleration data, to assess balance and concussion symptoms while an athlete performs clinical balance tests with an iPad attached to the waist (see photo, p. 12). The app analyzes data to provide objective and specific measures of cognitive and motor function as well as balance and postural stability. Validation studies have shown that the app measures balance and postural stability with an accuracy equivalent to that of the system considered the gold standard for such testing (but which is expensive, large and nonportable). The concussion-related factors assessed by the app include:

- Information processing
- Reaction time (both choice and simple)
- Working memory
- Dynamic visual acuity
- Postural stability
- Visual memory

Figure. “Performance polygon” plot for a subject who sustained a head injury on May 10, 2012 (see text for details on polygon tool). (CAP = cognitive assessment profile; SRT = simple reaction time; CRT = choice reaction time; VOR = vestibular ocular reflex; BESS = Balance Error Scoring System)

Athletic trainers have used the Cleveland Clinic Concussion (C3) iPad app to conduct baseline assessments of motor and cognitive function in nearly 6,000 youth athletes who play contact sports in Northeast Ohio (left). The app works by collecting data to assess balance and concussion symptoms while an athlete performs clinical balance tests with an iPad attached to the waist (middle). After baseline data are collected, the C3 app can be deployed in the locker room or on the sidelines for immediate concussion assessment if the athlete sustains a head injury. The functions assessed by the C3 app also include those evaluated through trail-making tests performed with a stylus (right).

Into the Clinic and onto the Field

After the validation studies, we systematically evaluated the C3 app for use in the performance of a clinical balance test often used in concussion: the Balance Error Scoring System (BESS). During BESS testing, subjects stand on varying surfaces and in varying postures to allow assessment of their processing of visual information, somatosensory (tactile) information and vestibular information from the inner ear. Whereas the traditional BESS test depends on a clinician’s subjective judgment, our study showed that the C3 app enables highly objective, quantitative BESS scoring that is also more sensitive than scoring by clinical observation alone, allowing greater discrimination between various concussive conditions. This study is now in press.

Next came a preliminary field study using the C3 app to gather baseline postural stability and functional data from 120 Cleveland-area high school and college athletes. The aim was to provide a benchmark to compare against if any athletes later sustained concussion. Twelve of these athletes suffered concussions during the season studied. We have learned from these 12 cases that concussion appears to leave a distinct “fingerprint” in different individuals in terms of the functions most affected. For instance, some individuals have substantial impairment in dynamic visual acuity while others have none, and some individuals suffer major balance impairments while balance is unaffected in others. We are also examining the rate of recovery of these affected functions over time to see how that fits into the broader concussive fingerprint. A manuscript on this study is in development.

‘Performance Polygon’ Guides Clinical Management

Our studies of functional return following concussion are facilitated by a method of data visualization we call the “performance polygon.” It plots an individual’s scores in nine performance domains (Figure) on the first post-concussion iPad assessment and periodically thereafter to allow easy visual monitoring of recovery to baseline levels (outer trace in Figure) over time. Depicting all domains in a single view makes the relative impairments in — and rates of recovery of — various domains readily apparent. This is valuable to clinicians for pinpointing the functional domains of concern and guiding the most appropriate therapy, and it helps patients easily understand what the treatment priorities are and why.

The clinical utility of this polygon tool underscores the importance of obtaining the athlete’s baseline assessment as well as assessments immediately after the injury and then frequently thereafter to monitor recovery.

Equally important is complete documentation of what happened at the time of injury, which the C3 app enables by providing the athletic trainer with a comprehensive questionnaire that elicits essential information about the incident and initial symptoms, which may later be valuable to a treating physician. It does so in a systematic way using drop-down menus and numeric coding to allow direct integration into the electronic medical record. The data are also integrated into Cleveland Clinic’s Knowledge Program interactive clinical database, which promotes management using our Concussion Carepath, an online evidence-based protocol designed to reduce variability of care across the health system and improve patient outcomes.
More Apps for That: Potential Additional Uses of the Cleveland Clinic Concussion App

Cleveland Clinic is exploring more ways to use the Cleveland Clinic Concussion (C3) iPad app, or adaptations of it, in additional neurologic conditions and to improve research efforts. Here are a few examples.

**Therapy guidance through precise assessment of impairment.**
The app’s ability to simultaneously assess motor function, cognitive function and balance opens the door to promising applications across a number of other neurologic disorders. Because virtually all daily activities combine cognitive and motor functions, there is value in being able to break down overall task performance into its cognitive and motor components, particularly for patients with conditions that can affect both, such as Parkinson disease (PD). The C3 app can deliver such value. For instance, a subject can use it to take a trail-making test with a stylus on the tablet screen (see photo on this page). The touch-screen functionality allows capture of data on the exact position of the stylus at discrete times, which enables us to differentiate speed of movement between dots (motor component) from time spent searching for the next dot without movement (cognitive component). Such insight can guide PD management based on how much a patient’s functional deficit is due to motor impairment, which will likely respond to drugs such as levodopa, as opposed to cognitive impairment, which will not.

**Early disease detection in PD.**
Using the app for testing of postural stability and cognitive and motor function may help detect early-stage PD. The app could be used for periodic testing of at-risk individuals to allow earlier diagnosis — and thus earlier and perhaps more successful intervention — as well as for sensitive longitudinal tracking of early disease progression.

**Improving research and clinical efficiency.**
Giving patients and study participants a relatively inexpensive device equipped with apps for clinical assessment can facilitate research and streamline care. Patients can use the device to complete tests remotely from home on a scheduled basis, thereby reducing in-person visits. This saves time and money for patients and providers even while making more frequent monitoring possible. Likewise, fewer in-person visits for data readings can allow substantial expansion of the patient recruitment area for clinical trials, which promises to speed scientific discoveries and their translation to clinical care.

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**Current and Next Steps**

In 2012, Cleveland Clinic has used the C3 app to complete baseline functional assessments of nearly 6,000 young athletes who play contact sports (e.g., football, men’s and women’s soccer) at the more than 50 high schools and colleges across Northeast Ohio that have Cleveland Clinic certified athletic trainers. We are using these baseline data to realize our vision for optimal care should any of these athletes sustain a head injury. We are also making the C3 app available for post-injury assessment among an additional 6,000 young athletes who are managed by our athletic trainers but who play noncontact sports or have not yet been scheduled for baseline assessment.

Our next aim is to explore broader deployment of the app, together with our Concussion Carepath, for coordinated use by schools and hospitals across the country. Together these highly transferable tools have the potential to take much of the guesswork out of concussion assessment and care, allowing physicians to make safer return-to-play decisions.

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Understanding Long-Term Seizure Outcomes of Epilepsy Surgery: Is a New Framework at Hand?

By Lara Jehi, MD

Many new opportunities are evolving in the field of surgical outcomes research to bridge the gap between the medical and surgical treatment of epilepsy. Recent findings from the Outcomes Research Program in Cleveland Clinic’s Epilepsy Center suggest that patterns of seizure recurrence after epilepsy surgery provide the best clue to understanding the mechanisms of epileptogenesis. Other findings have raised a number of compelling questions: Is the quintessential stroke mantra, “time is brain,” applicable to the timing of epilepsy surgery as well? And could anti-epileptic drug (AED) management represent the most efficient way to improve how we plan temporal lobe epilepsy surgery? This article reviews how our program is drawing on our surgical patient base over the past 15 years to shed light on these and other issues surrounding long-term seizure outcomes.

Defining Drug Resistance Downward

Epilepsy affects 2 to 3 million people in the United States and accounts for a disability burden comparable to that of breast and lung cancer. While AEDs control seizures in most cases, 25 to 30 percent of patients suffer from drug-resistant epilepsy, which carries an increased risk of self-injury, falls and fractures as well as a dramatic increase (up to 24-fold) in the risk of sudden death. The International League Against Epilepsy recently defined drug resistance as failure to achieve complete freedom from seizures after appropriate trials of only two adequately chosen AEDs. This definition recognizes that further medication trials have less than a 5 percent chance of achieving remission while surgical removal of the epileptic focus clearly represents a much superior option, as demonstrated by level I evidence from a randomized clinical trial.

Questions Born out of 15 Years of Data

Long-term seizure outcome data collected from 1,418 patients who underwent epilepsy surgery at Cleveland Clinic over 15 years (1996-2010) illustrate the sustained effectiveness of this surgery, with close to half the patients retaining complete freedom from seizures more than a decade after the intervention. Additionally, epilepsy surgery significantly improved these patients’ quality of life and functional status. However, these long-term outcomes also raise many questions, with the most challenging being:

- If the epileptic focus is indeed successfully removed through surgery, why would seizures recur at all after the resection?
- Why do patients who were having multiple weekly or even daily seizures before surgery become completely seizure-free after the resection, only to have seizures recur several years later?

The key to improving surgical outcomes lies in understanding the mechanisms of surgical failure, and that is where our research has focused over the past few years.

Seizure Recurrence: Two Distinct Mechanisms?

Detailed analysis of the longitudinal seizure outcomes following temporal, frontal and posterior quadrant resections in our patient population reveals that regardless of the type of surgery, half of all patients with recurrent postoperative seizures experience their initial seizure recurrence within the two to six months immediately after surgery, while the remaining half face it within the subsequent 10 to 15 years. This consistent observation of two separate “early” and “late” phases of seizure recurrence suggests two distinct mechanisms of recurrence.

Careful analysis of the characteristics of postoperative seizures shows that early-phase recurrent seizures are more likely to be drug-resistant from their onset and to arise in foci distant from the surgical bed. Predictors of early seizure recurrence include markers of diffuse and poorly localized epilepsy such as bilateral abnormalities on brain MRI, the need to obtain ictal and functional mapping through invasive EEG recordings, and the presence of interictal epileptiform abnormalities on postoperative EEG. This suggests that these early-phase surgical failures are likely due to inaccurate localization of the epileptic focus or its incomplete resection.

Conversely, late-phase postoperative seizure recurrences, manifesting for the first time several years after surgery, are usually milder, less frequent, easier to control with AED adjustment and most often seen in patients with no clear pathological substrate for their operated epilepsy. In other words, late seizure recurrences behave clinically much like new-onset epilepsy, suggesting that they may be due to the maturation of a new epileptic focus, or epileptogenesis.

New Framework for Understanding Surgical Outcomes

Introducing this framework of two distinct phases and mechanisms of surgical failure (Figure) represents a drastic change from traditional approaches to studying surgical outcomes and developing methodologies to improve the results of epilepsy surgery. Traditionally, efforts at improving surgical outcomes have centered exclusively on improving...
imaging and electrophysiological technology aimed at localizing the epileptic focus. Our work highlights the untapped potential of modifying medical therapy postoperatively to alter epileptogenesis and reduce the risk of subsequent seizure recurrence.

In a recently published study, we showed that the use of levetiracetam, an AED with strong basic science and animal model data on its anti-epileptogenic effects, may reduce the risk of postoperative seizure recurrence following temporal lobe epilepsy surgery. Specifically, we found that 47 percent of patients receiving levetiracetam were completely seizure-free more than five years after surgery compared with 28 percent of patients whose AED regimens did not include levetiracetam.

On the other hand, we also found that the duration of epilepsy, a reflection of the extent and intensity of the epileptogenic potential, is an independent risk factor for seizure recurrence following extratemporal lobe epilepsy surgery (Simasathien et al, in preparation). This finding highlights the importance of early surgical treatment of intractable focal epilepsy and strengthens the hypothesis that modifying or interrupting epileptogenesis may be the future of improving surgical outcomes.

Dr. Jehi is Head of the Outcomes Research Group and Director of Clinical Research in Cleveland Clinic’s Epilepsy Center. She also serves as Associate Program Director of the Clinical Research Unit. She can be contacted at 216.444.3309 or jehi@ccf.org.

REFERENCES
Large Randomized Trial to Assess Physical Activity Promotion in Multiple Sclerosis

By Matthew Plow, PhD

In the pursuit of a cure for progressive neurological disorders such as multiple sclerosis (MS), we must not forget that people cope with the physical and psychological effects of MS on a daily basis. In addition to biomedical and pharmacological research to stop or slow disease progression, there is a need for self-management research to identify strategies to help people cope with the physical impairments and psychological effects of MS. Promoting long-term engagement in physical activity may be one such strategy, and it’s one our research team at Cleveland Clinic is excited to be part of.

Growing Recognition of the Benefits of Exercise in MS

It was once recommended that people with MS should not engage in physical activity because it could exacerbate the disease process. This initial recommendation was probably based on the observation that people with MS often experience a temporary worsening of symptoms, such as fatigue, after a single bout of physical activity. However, increases in symptoms usually subside after rest, and there is no published evidence to suggest that it is unsafe for people with MS to engage in physical activity. In fact, cumulative evidence from systematic literature reviews now indicates that physical activity has beneficial effects on mobility and health-related quality of life among adults with mild to moderate MS impairment.

At the same time, research indicates that the population with MS is extremely inactive. It is understandable that common MS symptoms can compromise patients’ ability and motivation to undertake physical activity. Yet, given the documented benefits of engaging in physical activity, the question becomes how to design interventions to promote long-term adherence to physical activity programs.

The idea is that if people with MS can effectively manage their fatigue, they may be more likely to engage in physical activity.

A Telehealth Trial Supported by the MS Society

The National Multiple Sclerosis Society has recognized the importance of asking such questions. It has funded our research team — which includes collaborators Marcia Finlayson, OT, PhD, and Robert Motl, PhD, from the University of Illinois and Francois Bethoux, MD, of Cleveland Clinic’s Mellen Center for Multiple Sclerosis Treatment and Research — so that we can conduct the largest randomized clinical trial to date examining the effects of an intervention to promote lifestyle physical activity among adults with mild to moderate MS impairment. The study’s specific purpose is to examine the effectiveness of a telehealth intervention that supports individuals with MS in managing fatigue and increasing physical activity.

The study is novel because it represents a multidisciplinary effort to merge two promising lines of research in MS: fatigue management and physical activity promotion. The idea is that if people with MS can effectively manage their fatigue, they may be more likely to engage in physical activity.

Study Design and Rationale

The goal is to recruit approximately 189 people with MS in Ohio to participate in the study. Participants will be randomized to one of three interventions: (1) physical activity only (comparison intervention arm), (2) fatigue management plus physical activity (treatment intervention arm) and (3) social support (“contact control” arm). Each arm involves a 12-week intervention period followed by a 12-week noncontact period to determine whether the effects persist.

Intervention strategies to promote lifestyle physical activity will consist of a novel yet simple approach: encouraging goal-setting and self-monitoring with a pedometer. Intervention strategies to reduce fatigue impact will involve teaching energy-conservation principles (e.g., emphasizing the importance of rest throughout the day), setting priorities, activity analysis and modification, and living a balanced lifestyle. No intervention arm is focused solely on fatigue management because there is ample evidence supporting this intervention, and adding such an arm would add needless recruitment challenges. The “contact control” intervention involves exposure to topics typically discussed in expert-led support groups, such as information on MS, disease-modifying medications, preventive screening, community organizations, nutrition and supplements, cognitive problems, and recognizing symptoms of depression and chronic stress.

Because all interventions will be conducted over the telephone, they promise to offer accessibility and potential for dissemination if shown to be effective.

Ultimately, we hope to demonstrate through this randomized trial that cost-effective telehealth intervention strategies to promote physical activity and reduce fatigue impact will improve quality of life and overall well-being in individuals with MS.

Dr. Plow is a project scientist in the Department of Biomedical Engineering and the Department of Physical Medicine and Rehabilitation. His research interests are promoting initiation and maintenance of physical activity for persons with chronic disabling conditions, developing and testing outcome measures, and promoting self-management of symptoms. He can be contacted at 216.445.3288 or plowm@ccf.org.
New ‘Hyperacute MRI Protocol’ Improves Patient Selection and Outcomes for Intra-Arterial Stroke Therapy

By M. Shazam Hussain, MD, FRCP(C), and Paul Ruggieri, MD

Because patient selection is critical to the success of intra-arterial (IA) stroke therapy, Cleveland Clinic’s Center for Neuroimaging and Cerebrovascular Center recently established a “hyperacute MRI protocol” for the assessment of potential candidates for IA therapy. Preliminary results have shown that this protocol has reduced by half the number of patients who are treated with IA therapy, and this has in turn resulted in better outcomes for all patients, regardless of the type of treatment they receive.

The Need for an Alternative to IV Treatment

It is important to identify good candidates for intra-arterial therapy because the alternative, intravenous therapy with tissue plasminogen activator (IV tPA), has its limitations. Although IV tPA is effective in many cases, substantial numbers of patients still die or are left with a severe disability despite treatment. This is particularly true in cases of a sudden occlusion of a large artery — i.e., the internal carotid artery, middle cerebral artery or basilar artery. In these cases, recanalization rates with IV tPA are low, ranging from only 10 to 20 percent.

In response to the limited effectiveness of IV tPA in patients with large-artery occlusions, IA stroke therapy with thrombolytic agents or mechanical thrombectomy emerged as an important option in this group of patients. Still, while recanalization rates with IA therapy have approached 90 percent, many major studies have shown that patient outcomes remain poor.

Rationale for the New Protocol

It was this contradiction — highly effective recanalization rates accompanied by poor patient outcomes — that provided the impetus for a new model for acute stroke management based on more stringent criteria for patient selection. In the past, patient selection for IA therapy was based on the results of CT and CT angiography (CTA). These modalities, which are readily available in most cases, are mainly used to rule out acute intracranial hemorrhage and to identify large-vessel occlusions. However, CT and CTA have their drawbacks. For example, early ischemic changes seen on CT — such as the subtle loss of gray/white matter differentiation and sulcal effacement from cytotoxic edema — can provide clues to the area of ischemic damage. However, the sensitivity of CT for acute ischemia is relatively low, especially very early in the course of acute strokes. Therefore, it is likely that many patients will end up proceeding to IA therapy when they already have a large amount of ischemic tissue that was not apparent on CT.

Unlike CT/CTA, MRI is very sensitive for acute ischemia. It can demonstrate strokes within 30 minutes of acute vessel occlusions. However, the general use of MRI for stroke assessment is limited by a lack of availability in some settings. Also, the benefits of MRI must be weighed against the additional time it requires in a situation where rapid treatment is critical. Nonetheless, for the evaluation of candidates for IA stroke therapy, the benefits of MRI, particularly DWI, as a means of

Figure 1. Left: Comparison of mortality data among all patients considered for intra-arterial (IA) therapy in the pre- and post-MRI periods. Right: Comparison of mean pre- and post-MRI era modified Rankin scores for all patients with acute strokes considered for IA therapy.
precisely identifying the ischemic core may outweigh the inherent limitations, as shown by our initial experience.

Pre/Post Comparison Shows Improved Survival

We instituted our hyperacute MRI protocol on April 30, 2010; enough time has passed to allow us to present preliminary outcomes data. We retrospectively analyzed outcomes in 267 patients: 171 who presented from July 2006 through April 29, 2010 (pre-MRI era), and 96 who presented from April 30, 2010, to June 30, 2011 (post-MRI era). The pre-MRI group was made up of 95 men and 76 women (mean age, 67 ± 15 years); 92 percent of these patients (n = 158) received IA therapy. The post-MRI group included 43 men and 53 women (mean age, 68 ± 15 years); only 45 percent (n = 43) received IA therapy.

Mortality was significantly lower across the entire group of patients in the post-MRI era (i.e., those who proceeded to IA therapy and those who had not). Mortality during the pre- and post-MRI eras was 23 percent and 16 percent, respectively (P < .05) (Figure 1). At 30-day follow-up, the mean modified Rankin score among those considered for IA therapy was 4 in the pre-MRI group and 3 in the post-MRI group (P < .05) (Figure 1).

By reducing the percentage of IA-treated patients by roughly half with the hyperacute MRI protocol, we were able to achieve significantly greater survival in acute stroke patients regardless of the specific type of therapy received. We believe the benefit was attributable to the fact that many patients who received IA therapy were found to have large infarcts on DWI that were not apparent on CT. Also, survival improved in the post-MRI era even though the time required to obtain an MRI delayed the start of angiography (median delay, 50 minutes).

Future Directions: Careful Patient Selection Is Key

These findings are of critical importance for patients with acute stroke. We believe that future trials of IA therapy should follow our lead and focus on more stringent patient selection, ideally guided by MRI. Our data suggest that we must select patients carefully to avoid interventions for patients who will not benefit from or who will be negatively impacted by a high-risk and/or costly procedure. Careful selection criteria may also identify those patients who present with little or no permanent tissue damage but who will have a large volume of tissue at risk if they are not treated urgently with IA therapy (Figures 2-4).

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REFERENCE

Interdisciplinary Rehabilitation Program Successfully Treats Patients with Chronic Pain and Coexisting Chemical Dependency

By Giri Sweis, PsyD; Kelly Huffman, PhD; Elizabeth Shella, MA; Edward Covington, MD; and Judith Scheman, PhD

Chemical dependency is increasingly prevalent in people with chronic pain. Some studies suggest that as many as 32 percent of chronic pain patients who take opioids have an opioid use disorder, and multiple investigations have shown that up to 58 percent of patients abuse their opioid prescriptions.1,2 Both chronic pain and chemical dependency are difficult to treat. When these conditions occur in the same patient, many providers are at a loss as to how and in what order to approach the problems.

One clinical center that is fully equipped and staffed to manage these patients is Cleveland Clinic’s Neurological Center for Pain. Our intensive three- to four-week outpatient Chronic Pain Rehabilitation Program (CPRP) aims not only to reduce pain and chemical dependency but also to restore physical and social function, normalize mood, improve coping and restore vocational competencies. Our interdisciplinary team includes specialists in pain medicine, nursing, neurology, psychology, psychiatry, and physical and occupational therapy. Treatment involves education, medication management (including weaning from habituating medications such as opioids and habituating sedatives), training in coping skills, and individual and group psychotherapy, in addition to physical and occupational therapy. The Neurological Center for Pain is recognized by the American Pain Society as a Clinical Center of Excellence in Pain Medicine.

Chemical Dependency Need Not Be a Barrier to Pain Rehab Success

CPRP outcomes data demonstrate the extent to which we are able to successfully address chronic pain and chemical dependency simultaneously. We reviewed the records of 797 patients who completed the CPRP between 2007 and 2010. In addition to chronic pain, 39 percent of them had a concomitant chemical dependency. Outcomes measures included medication use, pain severity, pain-related functional impairment, anxiety and depression. We found that patients experienced significant improvements in pain, function and mood. On average, our patients experienced a 65 percent reduction in pain-related functional impairment and complete normalization of mood.

On admission to the CPRP, 77.5 percent of patients had been taking prescription opioids or habituating sedatives. Upon completion of the program, 89 percent had been successfully weaned from all habituating medications. It is noteworthy that those with concomitant pain and addiction generally fared no worse than those who had only chronic pain. Indeed, there was some evidence that patients with chemical dependency actually experienced greater improvements in some areas. For example, at program completion, these patients experienced a 59 percent reduction in pain, as opposed to a 51 percent reduction among those without chemical dependency. Moreover, although patients with chemical dependency had significantly higher levels of anxiety and depression when they started the CPRP, their mood at follow-up was not significantly different from that of the nondependent patients.

Treatment Gains Maintained over the Long Term

We are also encouraged by the long-term maintenance of treatment gains. A total of 234 patients completed a self-report survey 12 months after completion of the CPRP. It showed that patients continued to report significant improvement over the long term, regardless of whether they had a comorbid chemical dependency diagnosis. Although the

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Figure 1. Pre- and post-treatment depression scores in the two groups.

Figure 2. Pre- and post-treatment pain severity scores in the two groups.
patients with chemical dependency had a slightly higher mean depression score (in the mild depression range) at 12 months (Figure 1), there were no significant differences between the two groups in pain severity (Figure 2), pain-related functional impairment (Figure 3) or anxiety (Figure 4).

An especially gratifying finding was that, on average, only 21 percent of those who had been weaned from habituating medications had resumed their use (Figure 5), and there was no statistical difference in the rate of resumption between those with and without a chemical dependency. These results are particularly promising when compared with results of studies of recreational opioid dependence, which have suggested relapse rates as high as 91 percent in abstinence-based treatment programs.3

Overall, our cumulative data suggest that our multidisciplinary CPRP confers benefit to a large preponderance of those who seek relief from this intractable condition. It is especially encouraging to see such strong and long-lasting improvement in patients with coexisting chemical dependency.

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REFERENCES

Microscopic Magnetic Stimulation Shows Promise as an Alternative to Other Brain Stimulation Modalities

By John T. Gale, PhD

Electrical stimulation and transcranial magnetic stimulation (TMS) have proven to be beneficial for patients with certain neurologic disorders, including Parkinson disease, essential tremor and dystonia. These treatments are also being explored as an alternative to surgery for patients with other neurologic conditions, such as obsessive-compulsive disorders. Moreover, electrical stimulation has been shown to be valuable for investigating the function of the nervous system ever since it was introduced by Galvani in the 1700s.

Yet despite the success of these technologies, a few technical and practical limitations have impeded our ability to take advantage of their full potential. To overcome these limitations, Cleveland Clinic’s Center for Neurological Restoration is evaluating a new brain stimulation technology called microscopic magnetic stimulation (μMs). Our findings thus far provide a rationale for the further exploration of μMs as a prospective therapeutic tool with both clinical and preclinical applications.

How the Technology Works

This new μMs technology involves the use of sub-millimeter-sized coils (Figure on p. 22 illustrates the size of a coil relative to a pencil) to avoid the metal contact needed to modulate brain activity with electrical stimulation modalities. In contrast to the coils used in TMS, μMs coils’ small size allows them to be implanted directly into the brain or in close proximity to the brain surface. Once implanted, coils can be supplied with electrical current via implanted impulse generators, similar to the model used for cardiac pacemakers. When current is applied to a coil, a magnetic field is generated around the coil that penetrates into the tissue. As the magnetic field spreads, it causes a change in electrical charge around the brain tissue that can make brain cells change their activities.

Induction Coil Is Not in Contact with Brain Tissue

One of the potential uses of μMs is to improve the delivery of invasive electrical stimulation. The principal problem with standard techniques such as deep brain stimulation (DBS) is that the metal stimulation conductor comes into contact with the brain tissue. This interface induces a neuroinflammatory response and gliotic encapsulation of the contacts, which can affect charge densities at the site of stimulation and possibly reduce therapeutic efficacy.

One way to overcome the reduction in charge densities is to simply increase the amplitude of stimulation. However, increasing stimulation amplitudes might result in an inadvertent activation of surrounding structures, which can lead to stimulation side effects. Two such side effects are paresthesias and diplopia secondary to inadvertent activation of the medial lemniscus and corticobulbar fibers, respectively. In addition to these potential inflammatory complications, performing MRI procedures on patients with implanted DBS leads calls for specific precautions to be taken. Reports indicate that the heating of the leads may cause tissue damage. As is the case with the inflammatory processes, this heating occurs as a result of the direct interface between the stimulation contact and the tissues of the brain. The cabling of the DBS lead can absorb the radiofrequency energies produced by the MRI scanner and transfer this energy in the form of heat to the brain at the site of the leads.

In contrast, μMs avoids these limitations by keeping the induction coil out of direct contact with the tissue. The coil can be enclosed in a biocompatible coating (such as a parylene coating), which mitigates both the inflammatory processes and potential MRI hazards.

Tiny Size Allows for Implant Flexibility

Although direct electrical stimulation (stimulation of the brain through the scalp) and TMS offer advantages over invasive technologies, they have limited applications. Specifically, both technologies require precise contact placement in order to modulate specific brain regions. Therefore, highly trained personnel are needed to ensure that the contacts are appropriately positioned to maximize outcomes. In addition, TMS requires large power sources to drive the magnetic fields because the coils are large and situated far from the stimulated tissues. As a result, TMS therapy requires that patients make repeated office visits to receive treatment. Together, these drawbacks limit the feasibility of long-term neuroprosthetic applications, reducing both their efficacy and accessibility.

In contrast, the small size of the μMs coils enables our neurosurgeons to implant them close to (either within or adjacent to) the specific brain targets. Also, the μMs devices use far less energy than do the TMS devices. Another area in which μMs has proven to be effective is in activating the local neural circuitry of the retina in vitro.

In Vivo Evidence of Trans-Synaptic Neuronal Activation

In our current studies, we have demonstrated that μMs technology is capable of activating neuronal circuitry on the systems level with the use of an in vivo rodent preparation. Specifically, μMs of the dorsal cochlear nucleus activates the neurons of the inferior colliculus (Figure). Additionally, we have demonstrated the efficacy and characteristics of trans-synaptic activation using different amplitudes of stimulation, where higher amplitudes reduce latencies and decrease variability. These findings represent an important step toward translation to clinical use, as they are the first to demonstrate that μMs is capable of trans-synaptic neuronal activation in vivo.
The possibility that µMs could be used as an alternative for other stimulation applications — such as in cochlear, visual and muscular prosthetic contexts — remains to be tested. We look forward to contributing to such investigations, as well as to exploring the use of µMs as a potential tool for investigating the mechanisms that underlie electrical and/or transcranial magnetic stimulation.7

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REFERENCES


Thermoregulatory Sweat Testing: A Valuable Aid to the Diagnosis of Autonomic Disorders

By Robert W. Shields Jr., MD

Thermoregulatory sweat testing (TST) is a unique test of autonomic function that can evaluate sudomotor function over the entire anterior body surface. As such, it is a valuable test for detecting autonomic and other neurological disorders that cause sweating dysfunction, such as anhidrosis and hyperhidrosis.

Although TST has been used in some form for decades, the technology required to perform the test today has such complex technical demands that TST is available only in a handful of medical centers in North America. Since July 2011, TST has been added to the numerous other tests of autonomic function available in the Autonomic Laboratory of Cleveland Clinic’s Center for Syncope and Autonomic Disorders. This center represents a collaboration between Cleveland Clinic’s Neuromuscular Center and the Department of Cardiovascular Medicine to provide comprehensive care to patients with autonomic disorders. TST is an important addition to our state-of-the-art testing facility, enabling us to evaluate patients with autonomic disorders with greater accuracy and precision.

Implementing TST is a costly and complex undertaking. The heating cabinet used for the test must be custom designed and built. The laboratory that houses the cabinet must provide special electrical, plumbing and ventilation connections. Furthermore, the TST lab requires access to shower facilities. Despite these challenges, the TST lab was established so we could provide our patients with the full complement of tests that may be needed for the diagnosis of autonomic disorders.

How TST Is Administered

Patients undergoing TST are contacted before the test to assess their medications and special needs in preparation for the test. Some medications that interfere with sweating may need to be discontinued prior to the test, if possible. Once in the laboratory, the patient is provided with disposable swimwear for the test. The patient lies on a gurney-sized table and his or her exposed skin is coated with an indicator powder that turns color when it interacts with sweat. The patient is then positioned in the heating cabinet, which is constructed of wood and clear plastic panels, a design that minimizes concerns about claustrophobia. The cabinet provides a controlled thermal stimulus of 115 degrees Fahrenheit and 40 percent humidity. Most patients begin sweating within 10 minutes and spend 30 to 45 minutes in the cabinet. When sweat interacts with the powder, the latter turns from light tan to dark purple, revealing which areas of the body are sweating and which are not (Figure 1).

During the test, body and skin temperatures are monitored continuously (Figure 2). When patients demonstrate maximum sweating or their body temperature reaches the maximum allowable level, they are removed from the cabinet. A camera located in the cabinet dome takes photographs of the body during the test, which are used to analyze the patient’s sweating pattern.
indications and diagnostic capabilities

TST can evaluate both preganglionic and postganglionic function, providing a comprehensive assessment of thermoregulation in both the CNS and the efferent peripheral autonomic nervous system that innervates the sweat glands. Thus, it can detect abnormalities in any part of the thermoregulatory system.

The indications for TST include small fiber and autonomic neuropathies, radiculopathies and mononeuropathies, and central autonomic disorders such as multiple system atrophy, Parkinson disease with autonomic dysfunction, and a pure autonomic failure. TST has shown promising results in differentiating multiple system atrophy from Parkinson disease, especially in the early phases of these disorders.

Normal sweating patterns have traditionally been defined as one of three types. Type I is a pattern of general heavy sweating in all areas and is typically seen in young men. Type II involves heavy general sweating with some reduced sweating in proximal areas of the limbs; it is often seen in women. Type III is characterized by general sweating with some reduction in the proximal and distal limbs and is often seen in older adults of both sexes.

Abnormalities on TST are categorized by various patterns of anhidrosis. A distal pattern discloses reduced or absent sweating in a symmetrical, length-dependent pattern in the limbs and is typical of autonomic and small fiber neuropathies (Figure 3). Segmental patterns are characterized by larger zones of anhidrosis with sharp boundaries reflecting spinal cord levels or sympathetic dermatomes. Focal patterns reflect small zones corresponding to a peripheral nerve territory or isolated dermatomes. Regional patterns are larger areas of anhidrosis that do not have sharp borders and are most typical of a central autonomic disorder. A global pattern of anhidrosis indicates that greater than 80 percent of the skin is anhidrotic.

Use in Combination with QSART

TST can be used with quantitative sudomotor axon reflex testing (QSART), another sudomotor test offered in our laboratory, which evaluates how autonomic peripheral nerves that regulate sweat glands respond to indirect stimulation via capsules placed on the forearm, foot and leg. Compared with TST, QSART evaluates only postganglionic sudomotor function in a limited area of the body and is mostly used to detect autonomic neuropathy. When used together in the same patient, TST and QSART can differentiate preganglionic (CNS) disorders from postganglionic (peripheral nerve) disorders, an important distinction in providing accurate diagnoses. Moreover, when evaluating patients for autonomic or small fiber neuropathy, combining TST and QSART provides diagnostic sensitivity of greater than 90 percent.

The Future: New Research Opportunities, Expanded Access

TST is also useful in clinical research, enabling better characterization of patients for studies of autonomic disorders. As a result, we can now undertake new types of studies that increase our understanding of the entire autonomic system.

Over the past year, we have performed TST on a growing number of patients. Because TST greatly aids diagnosis, we plan to expand our testing schedule to accommodate more patients.

Dr. Shields is Head of the Autonomic Laboratory in Cleveland Clinic’s Neuromuscular Center. His specialty interests include autonomic disorders, autonomic nervous system disease and testing, electromyography and neuromuscular diseases. He can be contacted at 216.444.0855 or shieldr@ccf.org.
Mitochondria as a Link Between Inflammation and Neurodegeneration in Multiple Sclerosis

By Don J. Mahad, MD, PhD, and Ranjan Dutta, PhD

The gradual and irreversible decline in neurological function (progression) continues in patients with multiple sclerosis (MS) despite optimal use of immunomodulatory therapy. An increasing body of evidence from Cleveland Clinic and other institutions is establishing a role for mitochondria in the pathogenesis of MS and identifying mitochondria as potential therapeutic targets in progressive MS. This article summarizes that evidence and looks ahead to potential insights to be gained from in vivo study of CNS bioenergetics by high-field-strength magnetic resonance spectroscopy, soon to be available at Cleveland Clinic’s Mellen Center for Multiple Sclerosis Treatment and Research. Our hope is that such studies will help establish the relationship between mitochondrial defects and clinical and paraclinical parameters in MS.

A Need to Clarify the Neurodegeneration-Inflammation Relationship

MS is now also considered a gray matter disease in which cortical pathology, like white matter demyelinating lesions, starts early and correlates with clinical disability. Inflammation, in its many forms, is abundant within white matter foci during early-stage MS, associates with active demyelination and persists in a diffuse manner during the progressive stage of MS. Meanwhile, there is an incessant loss of neurons and axons in the MS brain and spinal cord. In progressive MS, neurodegeneration may be the direct result of inflammation and related to it, or it may be independent of inflammation. The progression of neurological disability despite immunomodulatory therapy has led to the hypothesis that neurodegeneration may be the primary event in MS and independent of inflammation. These fundamentally different concepts need to be addressed as part of the strategy to develop effective therapy for progressive MS.

Mitochondria Are Essential for Maintaining a Healthy Nervous System

Mitochondria are the powerhouse of neurons, which are reliant on aerobic metabolism. More than 90 percent of oxygen used to generate energy in the CNS is consumed by mitochondria—in particular cytochrome c oxidase, or complex IV of the mitochondrial respiratory chain. Mitochondrial DNA (mtDNA), the only non-nuclear DNA, encodes a number of functionally important components of the mitochondrial respiratory chain, which is made up of five complexes.

mtDNA is particularly susceptible to oxidative damage. Given the several hundred copies of mtDNA within a single cell, an induced mtDNA mutation must therefore increase to levels high enough (as a proportion of total mtDNA) to impact the activity of the mitochondrial respiratory chain as well as other well-recognized functions of mitochondria (calcium handling and production of reactive oxygen species). The expansion of one mtDNA mutation (deletion or point mutation), also known as clonal expansion of mtDNA, is the process by which the proportion of an mtDNA mutation increases relative to the total mtDNA in a single cell. The dramatic clinical phenotypes in patients with inherited or sporadic mtDNA mutations highlight the importance of mtDNA mutations in the CNS.

Gray Matter in MS Harbors Mitochondrial Defects

The first description of mitochondrial respiratory chain defects within the gray matter in MS originated from the laboratory of Bruce Trapp, PhD, at Cleveland Clinic. Levels of a number of nuclear DNA-encoded transcripts of the mitochondrial respiratory chain complexes were decreased in the MS motor cortex (without gray matter lesions), and these decreases were accompanied by significant impairment of respiratory chain activity. Furthermore, a subset of neurons in the MS cortex was shown to contain a high level of mtDNA deletions and showed a loss of complex IV activity. Although the basis of the mitochondrial defects within neurons in MS is not known, inflammation and demyelination are likely to play a role in the induction of the bioenergetic defects in MS.

Clonally Expanded Mitochondrial DNA Deletions in MS

Recent findings within the choroid plexus in MS and comparison with Alzheimer disease and Parkinson disease confirmed the presence of mtDNA deletions at high levels within single cells in MS. Importantly, the mtDNA deletions appeared to have reached high levels through clonal expansion rather than through continuous mutagenesis. Clonal expansion of mtDNA deletions within neurons is a phenomenon that is well-recognized in a number of neurodegenerative disorders, including MS. Ongoing studies indicate that the mtDNA deletions in MS, which are present in excess of the age-related changes, are restricted to the CNS and are more likely to be induced within the CNS rather than inherited as a diffuse phenomenon (involving multiple organs).

The concept of mtDNA deletion-led energy failure and neurodegeneration in MS holds that mtDNA deletions are induced by inflammation during the early stage (including subclinical phase) and continue throughout the course of MS while clonal expansion, the rate of which may well be influenced by the chronic inflammation in MS, leads to a high level of induced mtDNA deletions and a delayed biochemical defect within single cells (Figure). The prediction is that by the time the progressive phase of MS manifests, the resulting energy failure due to mtDNA deletions plays an important part in the pathogenesis of progression. The cells that are deficient or devoid of mitochondrial respiratory chain activity may be more susceptible to further insult and be particularly vulnerable in the presence of diffuse and chronic inflammation in MS.

In Vivo Measurement of Bioenergetic Changes in MS

Although autopsy tissue-based studies have been invaluable to discovery of the above observations, they are of limited value in determining the onset of the bioenergetic changes that are due to mitochondrial defects and their relationship to the clinical course of progressive MS. The hope is that in vivo measurement of bioenergetic parameters using techniques such as 31P magnetic resonance spectroscopy and high-field-strength (7T) MRI, soon to be available...
at Cleveland Clinic’s Mellen Center, will not only improve our understanding of bioenergetic disturbances in MS but also identify novel tools for measuring outcomes in clinical trials of progressive MS, particularly those that use agents targeting mitochondria as potential therapies for MS.

Dr. Mahad was a clinical fellow in Cleveland Clinic’s Mellen Center for Multiple Sclerosis Treatment and Research and a research fellow in the Department of Neurosciences, Lerner Research Institute, in 2010-2011. He is currently a senior clinical research fellow at the University of Edinburgh Centre for Neuroregeneration, Edinburgh, Scotland. He can be contacted at mahadd@doctors.org.uk.

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Phosphatase and tensin homolog (PTEN) is a tumor suppressor gene in mammals that is mutated in a subgroup of patients with autism spectrum disorder (ASD) who have significant macrocephaly.

Studies of the PTEN gene and related pathways, being conducted as part of the KL2 Multidisciplinary Clinic Research Training Program project at Cleveland Clinic, should shed light on three key research issues in ASD:

- Features associated with the likelihood of a PTEN alteration
- Logical targets for personalized treatment of ASD in children with a PTEN mutation
- Appropriate outcome measures for use in clinical trials to rapidly identify responses to personalized treatments

The project, a collaboration between the Center for Autism in Cleveland Clinic Children’s Hospital and the lab of Charis Eng, MD, PhD, in Cleveland Clinic’s Genomic Medicine Institute, has been examining the downstream neural and cognitive consequences of mutations in PTEN and related pathway genes in children with ASD.

**Mutation Linked with Macrocephaly**

Approximately 25 percent of children with autism have a large head, and 10 to 20 percent of those children have a PTEN mutation. Almost all patients with a PTEN mutation have macrocephaly because, as a tumor suppressor gene, PTEN functions as a regulator of cell growth and proliferation. Loss of PTEN therefore leads not only to cancer predisposition but also to disrupted regulation of neuronal and glial cell size and a corresponding increase in brain volume. Ongoing studies in these patients will enhance our understanding of molecular and biochemical changes as they relate to PTEN pathways, aiding in the selection of candidate molecular therapies and clinical trial endpoints.

**Two Pathways of Interest**

The two major pathways influenced by PTEN are the PI3K/AKT and MAP kinase pathways. The PI3K/AKT pathway is an important intracellular signaling pathway that plays a critical regulatory role in cell growth as well as in neuronal and dendritic function. The function of dendrites depends on the branching pattern of the dendritic tree. Excessive branching of dendrites has been observed with activation of the PI3K/AKT pathway, leading to an exaggerated number of neuronal connections, which in turn inhibits functional connectivity between brain regions.

**Wide Range of Related Investigations**

As part of the biochemical and molecular studies, blood and/or DNA samples undergo mutation scanning of the PTEN coding region, exon/intron boundaries and flanking intronic sequences up to approximately 40 bases, as well as undergoing promoter sequencing. The nature of any abnormalities is being determined by sequencing of the section in question. At least 100 participants with ASD and large head size, at least 100 with ASD without large head size and at least 40 healthy siblings are expected to be recruited for the study. Gene discovery studies are also being performed in a fourth group — patients with ASD who do not have the PTEN mutation.

Preclinical studies in PTEN-deficient mice conducted elsewhere have demonstrated that treatment with rapamycin can block neuronal hyperconnectivity and improve some features of autism.

Cleveland Clinic is also conducting neuroimaging studies to assess alterations in brain structure in ASD patients with the PTEN mutation (Figure). Because autism is a syndrome of biological disconnection between brain regions and a lack of coordination in processing between areas of the brain, the thought is that white matter fiber tracts that enable connections between brain regions may be dysfunctional.
Assessing an ASD Genetic Risk Tool

Findings from molecular and neuroimaging studies could help determine the potential benefits of early childhood screening for genetic mutations. To this end, the Center for Autism is also evaluating a genetic risk assessment tool for ASD in children as young as 12 months (see sidebar). A genetic risk assessment tool has the potential to ensure that high-functioning individuals with ASD continue to be appropriately identified. The study is designed to confirm the predictive value of established genetic markers and is a follow-up to completed retrospective studies.

Validating Proposed New Criteria for ASD Diagnosis

Using accurate diagnostic criteria is essential to genetic and neuroimaging studies of ASD. In preparation for the above investigations, we conducted a validation study of proposed new criteria for ASD as set forth in the fifth edition of the American Psychiatric Association’s Diagnostic and Statistical Manual of Mental Disorders (DSM-5), expected to be published in May 2013. In studying 14,744 siblings with and without ASD, we found that the proposed criteria had superior specificity to DSM-IV-TR criteria but had slightly lower sensitivity. We found that by eliminating one symptom, either a social or a repetitive behavior symptom, while still requiring at least one repetitive behavior symptom, sensitivity could be improved while reducing specificity only minimally.

Dr. Frazier is Director of Research for the Center for Autism as well as a staff member in Cleveland Clinic’s Center for Pediatric Behavioral Health and the Genomic Medicine Institute. His specialty interests include autism spectrum disorder, attention deficit/hyperactivity disorder and pediatric bipolar disorder. He can be contacted at 216.448.6440 or fraziet2@ccf.org.

Study Assesses Value of Genetic Tool for Identifying Autism Spectrum Disorder

Researchers with Cleveland Clinic’s Genomic Medicine Institute and Children’s Hospital are conducting the first prospective study of a novel, easy-to-use genetic risk tool that may help determine children’s risk for autism spectrum disorder (ASD) as early as 12 months of age.

The two-year observational study, which began in January 2012 and is still enrolling participants, has three main goals:

- Assess the value of the genetic tool, which involves a simple oral swab, in determining risk for ASD
- Identify genetic changes associated with ASD or other developmental disorders
- Examine whether genetic differences or changes may predict which children benefit from medications to treat developmental difficulties

We plan to enroll at least 600 children ages 12 months to 12 years in the case-control study — approximately 300 with ASD, 75 with attention-deficit/hyperactivity disorder or another developmental or psychiatric disorder, 100 healthy siblings of enrollees and 125 unrelated children without developmental or psychiatric disorders.

Participants undergo a gentle swab of the inside of the cheek to obtain cells for genetic testing. Parents or caregivers complete questionnaires to report medical and family history as well as the children’s symptoms and quality of life. The children also undergo speech and language evaluation. Our research team will then analyze the genetic test results against the participants’ symptoms and clinical features to look for any significant predictors.

The genetic tool, which is not yet commercially available, was developed by the biotechnology firm IntegraGen SA, which provided a grant to support this investigator-initiated study. It develops a risk score for ASD based on more than 60 single-nucleotide polymorphisms assessed for via the cheek swab.

This cheek swab-based test represents a potentially significant innovation because of its ease of use and its ability to be used early in life. Because it can enable assessment for ASD before the youngest children can be evaluated through play-based assessment (typically not until 18 months to 2 years of age), the tool may allow for earlier diagnosis of ASD. This, in turn, may enable more effective intervention for ASD during critical periods of brain development.
Pediatric brain tumors are a heterogeneous group of tumors with varying outcomes, prognoses and treatments. Surgery is often the first step in management, with the main goals being tissue diagnosis and, when possible, tumor resection. In many cases, a gross total resection can improve long-term progression-free survival and, in some instances, even be curative.

Certain tumors, such as gliomas, can pose various surgical challenges secondary to location and the extent of infiltration of normal brain tissue. The development of stereotactic navigation systems has made tumor localization and resection a very precise and calculated process. Despite this precision, confirming the extent of surgical resection via navigation is limited by intraoperative brain shifts and surgical manipulation. For tumors with ill-defined infiltrating borders, surgeons often must rely on their visualization, tactile sensation and experience to determine the boundaries of the resection cavity.

A ‘Second Look’ to Confirm Resection Goals

With the advent of the intraoperative MRI suite (IMRIS Neuro™ intraoperative suite) at Cleveland Clinic, we now have an extra tool to help achieve our surgical goals. The ability to obtain a high-quality scan to evaluate the surgical bed prior to closing allows the surgeon to go back and take a “second look” to confirm that surgical resection goals have been met and provide reassurance for both the physician and the family. This extra step in the surgical suite has the potential to spare a child an additional operation to remove a small residual tumor (Figure). A better resection may also delay or obviate the need for radiation treatment, an adjuvant therapy with significant potential side effects and developmental consequences.

Furthermore, because many children need sedation when undergoing MRI, the intraoperative MRI suite has been especially useful in allowing these patients to undergo pre-, intra- and postoperative imaging with a single administration of anesthesia.

Broadly Applicable

The intraoperative MRI suite is useful for both benign and malignant tumors. For low-grade processes such as pilocytic astrocytoma, a gross total resection, when possible, can result in a long-term cure. Even for higher-grade tumors such as medulloblastoma, more extensive tumor resection has been associated with better prognosis. Patients with less than 1.5 cm$^3$ of disease may be stratified as average risk and thus may require less adjuvant therapy than those considered high-risk because of greater tumor burden.

Our intraoperative MRI suite is also helpful in evaluating for potential complications early on. If there is concern about possible infarct or hemorrhage, an intraoperative scan can help minimize the delay involved in routine closing and transport, allowing for faster action.

On the Horizon: LITT in the Intraoperative MRI Suite

Looking ahead, Gene Barnett, MD, Director of Cleveland Clinic’s Rose Ella Burkhardt Brain Tumor and Neuro-Oncology Center, is using laser-induced interstitial thermotherapy (LITT) in adults to treat deep-seated tumors in difficult-to-access locations that were once deemed inoperable. This surgery is performed in the intraoperative MRI suite to allow for laser placement and real-time monitoring by MRI. Advances in this technology are evolving and will certainly have implications in the pediatric population as well.

Because of the many advantages the intraoperative MRI suite offers, its use is quickly becoming a standard practice for our pediatric patients. Longitudinal outcome studies may well show this to be a superior approach in the formidable task of treating pediatric patients with brain tumors.

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Chronic Pain After Spinal Cord Injury: Inhibition with Fibronectin in Rat Model Paves Way for Human Studies

By Ching-Yi Lin, PhD

A one-time intraspinal injection of fibronectin immediately after spinal cord injury (SCI) produces persistent inhibition of mechanical allodynia in an experimental rat model. This novel finding, recently published by a collaborative research group directed out of Cleveland Clinic’s Department of Neurosciences and Department of Physical Medicine and Rehabilitation,1 raises the prospect of a potential role for intraspinal fibronectin in inhibiting chronic pain after SCI in humans.

Why Fibronectin?

New approaches to inhibit chronic pain after SCI are desperately needed, as approximately 90 percent of the 1 million U.S. patients who have sustained SCI suffer from such pain. Many patients find the pain more debilitating than the paralysis that may result from SCI. Mechanical allodynia — pain from normally innocuous stimuli — is a common form of chronic pain related to SCI. The mainstays of current treatment for SCI-related pain lack sufficient strength for many patients and are limited by their addictive potential and significant side effects.

The mechanisms underlying pain following SCI are complex. Injury to the spinal cord increases the permeability of the blood-spinal cord barrier, which permits the invasion of inflammatory cells and the development of chronic pain. Also, dorsal column injury is known to reduce levels of serotonin, a neurotransmitter critical to pain perception, in the superficial dorsal horn.

We chose to study fibronectin, an endogenous glycoprotein that helps anchor cells in place, because it is known to support the survival and growth of neurons in the spinal cord. Two of fibronectin’s receptors (integrins α4β1 and α5β1) are involved in maintaining the vasculature and regulating infiltration of inflammatory cells into the spinal cord following SCI. These receptors are also present in primary afferent neurons that mediate pain.

Fibronectin-induced blockade of mechanical allodynia persisted over an eight-month observation period in the rat, which is comparable to 25 years in humans.

Our Study at a Glance

Rats that undergo dorsal column crush at the dorsal aspect of the C8 spinal cord segment develop mechanical allodynia over the ensuing five weeks — the pain emerges slowly, as it does in humans. For our study, dorsal column crush was induced by creating a lesion at C8 through insertion and squeezing of a forceps to a depth of 1 mm. Fibronectin (50 µg/mL) was then injected into the lesion space and both 1 mm rostral and 1 mm caudal to the lesion. We injected additional rats with the connecting segment-1 (CS-1) motif of fibronectin to assess whether this was responsible for fibronectin’s pain-blocking activity.

When we monitored the rats’ hind-paw withdrawal to assess sensitivity to non-noxious stimuli, we found that fibronectin injection resulted in a significant increase in withdrawal thresholds, indicating blockade of mechanical allodynia. We found that these effects were dependent on the CS-1 motif of fibronectin. Notably, this effect persisted over an eight-month observation period (Figure), which is comparable to 25 years in humans.

Further, fibronectin diminished inflammation and blood-spinal cord barrier permeability in areas surrounding the injury site, providing evidence that fibronectin treatment maintains the integrity of this barrier. No apparent adverse effects were observed with the fibronectin therapy.

Immunohistochemical Confirmation

Following dorsal column crush, glial fibrillary acidic protein (GFAP) and the microglia/macrophage marker ED1 were observed in areas surrounding the lesion, which suggests that astrocytes and inflammatory microglia and macrophages are activated in the days after SCI. Immunohistochemical staining showed that fibronectin treatment blocked SCI-induced upregulation of GFAP and ED1, which is consistent with a role for fibronectin in suppressing the inflammatory response after dorsal column injury and preventing secondary damage induced by inflammation.

Additional immunohistochemical testing confirmed a decrease in serotonin immunoreactivity in the superficial dorsal horn following dorsal column crush, suggesting that the pathogenesis of mechanical allodynia may involve serotonin. Notably, immunostaining also showed that injection of fibronectin into the rat spinal cord normalized the SCI-induced decrease in serotonin levels.
Future Research Directions: Delayed Administration, Other Pain Types

Our study, which was the first demonstration that fibronectin can induce plasticity in the spinal cord following SCI, is fueling further investigations at Cleveland Clinic to better elucidate the mechanisms underlying the development of SCI pain and better understand fibronectin’s pain-inhibiting properties. We aim to eventually test fibronectin treatment for chronic pain inhibition after SCI and in other disorders in humans, particularly in the setting of delayed fibronectin administration, given the impracticality of immediate treatment. We are encouraged by indications from studies to date that this therapy may be effective at later time points as well as very shortly after injury.

Our ultimate hope is that this research can lead to more effective treatment of other types of pain, including pain associated with inflammatory conditions, cancer pain and neuropathic pain.

Dr. Lin is an assistant staff member in the Department of Neurosciences in Cleveland Clinic’s Lerner Research Institute and a member of the Department of Physical Medicine and Rehabilitation research staff. She can be contacted at linc@ccf.org.

REFERENCE

Cognitive behavioral therapy for insomnia (CBT-I) targets maladaptive behaviors and dysfunctional beliefs and attitudes about sleep that promote and perpetuate chronic sleep problems. Unfortunately, the availability of CBT-I is limited, due to lack of access to trained clinicians, cost, and the difficulties of scheduling and completing a series of therapy sessions. To overcome these barriers to access, specialists in Cleveland Clinic’s Wellness Institute and Sleep Disorders Center have developed GO!® To Sleep, an online interactive program for delivery of CBT-I, with encouraging preliminary results.

Making CBT-I More Accessible

The 2005 National Institutes of Health State-of-the-Science Conference Statement on chronic insomnia concluded that CBT-I is as effective as prescription medication for the treatment of insomnia in the short term, with a suggestion that the beneficial effects of CBT-I last longer than those of prescription medications. Moreover, patients rate CBT-I interventions as more acceptable than pharmacotherapy. For these reasons, there is a critical need to make CBT-I more accessible to the general public.

Stepped care is a treatment delivery model based on the premise that interventions should vary in type and/or intensity. Under a stepped-care model, lower-cost interventions are attempted first, with more expensive and intensive treatments reserved for nonresponders.

One potential way to overcome the limited access to CBT-I is to incorporate Internet-based delivery of CBT-I into a stepped-care approach. Internet interventions are based on well-established individual CBT-I principles, incorporating the primary components of sleep restriction, stimulus control, sleep hygiene, cognitive restructuring and relapse prevention.

Several recent studies support the efficacy of Internet-based self-help CBT-I interventions. Ritterband and colleagues found that participants with primary insomnia who were randomly assigned to Internet-based treatment showed significantly improved sleep compared with wait-list controls, and these improvements were maintained at six months. Internet participants also achieved a significant decrease in wake time after sleep onset and an increase in sleep efficiency (hours slept divided by hours in bed) compared with controls. Similar improvements in measures of insomnia severity and sleep quality were obtained by Vincent and Lewycky, who evaluated a five-week Internet CBT-I intervention for participants with insomnia.

Interactive Online Program Individualizes Feedback

Taking these factors into account, we developed GO! To Sleep as an interactive online program to help patients improve their sleep from the comfort and privacy of their home. The six-week program incorporates the primary treatment components of CBT-I, including sleep restriction, stimulus control, cognitive restructuring, sleep hygiene, relaxation training and relapse prevention. GO! To Sleep users are sent daily emails encouraging them to log their sleep from the previous night. A daily sleep score is calculated, and individualized feedback and sleep improvement recommendations are provided.

After users log their sleep for the day, a lesson or article is provided on topics relevant to CBT-I, such as the basic science of sleep and why certain behaviors are detrimental to sleep. As the program progresses, users are encouraged to implement various strategies, such as stimulus control and sleep restriction, to begin improving their sleep patterns. Activities, tips and progress charts reinforce participants’ efforts to improve sleep quality. Throughout the program, users gain access to relaxation practices and other strategies to improve stress management and sleep. A mobile application is available for easy tracking of sleep patterns (Figure 1).

Promising Early Results

Preliminary results in the first 100 users who completed the program are promising. Sleep has improved most for patients with the greatest average total wake time (sleep-onset latency plus wake time after sleep onset) per night, representing more severe insomnia (Figure 2). Those with more than two hours of total time spent awake in bed per night at the start of the program had the most robust change in sleep efficiency, increasing from 65 percent to 81 percent, a 25 percent
relative improvement. In addition, those with more severe insomnia increased their total sleep time by one hour a night, on average. The share of participants with more than one hour of average total wake time per night decreased from 66 percent at the program’s start to 31 percent at its completion. Sleep efficiency increased from 76 percent to 86 percent, a clinically important improvement.

Assessment of the broader symptoms of insomnia using the Pittsburgh Insomnia Rating Scale, a composite measure of sleeping difficulty, sleep quality and insomnia-related distress, revealed a significant decrease in the average score, from 36 to 20, for all participants. The proportion of participants with clinical signs of insomnia (score > 20) decreased from 91 percent to 45 percent. The proportion who were very dissatisfied with their sleep declined from 63 percent to 18 percent, while the share who were quite satisfied increased from 8 percent to 47 percent.

Hope for Increased Access to CBT-I

The initial outcomes of our program, when added to those from previous research on online CBT-I programs, support the use of a Web-based method for delivering CBT-I. Internet applications have the potential to increase access to an effective but underused treatment option. The development of the GO! To Sleep online program is one of the many ways that Cleveland Clinic’s Sleep Disorders Center is expanding its comprehensive, multidisciplinary services for sleep disorders to the local community and beyond. For further information about our Web-based treatment program for insomnia, visit 360-5.com/sleep.

Dr. Drerup is a staff member in Cleveland Clinic’s Sleep Disorders Center and Department of Neurology. Her specialty interests include insomnia and other sleep disorders, anxiety disorders, depression, treatment adherence issues and psychological factors influencing medical conditions. She can be contacted at 216.445.9251 or drerupm@ccf.org.

REFERENCES

Computational modeling, which can be used to create virtual prototypes of the human anatomy, is a valuable tool for assessing physical structures. In the Spine Research Laboratory at Cleveland Clinic's Center for Spine Health, our investigators are developing accurate and fully validated computational models of the human spine. These models will allow us to study the behavior of the spine under various boundary and loading conditions. They will also provide clinicians with the ability to engage in virtual diagnosis, assessment and presurgical planning prior to the actual implementation of care. Virtual rendering of the spine can be useful to researchers as well as clinicians.

The Advantages of Spine Modeling

What makes computational modeling so vital is that traditional physical testing methods of the spine (both in vivo and in vitro) are less than ideal. For example, some techniques require the testing of animal or human cadaveric specimens in a machine, which is expensive and time-consuming. In addition, in vivo studies can pose ethical dilemmas and concerns about the accuracy of data and the extrapolation of results to human situations. Obviously, normal healthy human spines are not readily available for in vitro testing. Furthermore, the loads and muscle forces that are active in normal spine motion cannot be reliably replicated, and the distribution of internal stresses and strains within specific tissue components cannot be accurately measured.

A computer model of the spine has the advantages of providing useful information about a spine's response to external loads as well as the ability to predict the internal stresses and strains that occur (Figure 1). Spinal stability following the placement of various implants (e.g., an interspinous device) can be simulated and analyzed, providing clinicians with insight into the potential performance of specific implants before the actual surgery.

The Making of a Model

One of the models being developed in our Spine Research Laboratory is a multisegment lumbar spine. This model can be used to simulate and evaluate various clinical scenarios, such as the extent of degeneration, the biomechanical efficacy of surgical procedures (e.g., laminectomy and fusion) and the placement of implants for stabilization (Figure 2). Once a general model is validated, patient-specific versions can be developed quickly to aid clinicians in their decision-making process regarding the management of spinal ailments.

A ground-up approach is typically used for the development of a computerized spine model. It begins with the acquisition of CT scans to define the geometry of the vertebrae, which represent the hard-tissue elements. The geometry of the hard-tissue elements is converted to a 3-D model. Then the soft-tissue elements — intravertebral discs, ligaments and muscle — are added to the model, based on their CT dimensions. The upper and lower areas of the disc model are matched...
to the contours of the upper and lower endplates where the disc abuts the vertebrae. The insertion points for the ligaments are estimated on the basis of MRI data.

Following construction of the model, material properties are assigned to each of the distinct anatomic elements. In concert, all these elements establish a basis for insight into the relationship between an applied spinal load and the resultant deformation experienced by each of the spine’s component materials.

Spinal implants are designed to function as either fusion-enhancing devices or motion-preserving devices. The primary objective of fusion-enhancing devices is to stabilize a dysfunctional or damaged spinal segment by completely restricting its motion. Motion-preserving devices, such as an artificial disc, are intended to preserve the normal function of a spinal segment.

**Validating by Assessing Predictions**

Once one of these models is developed, it must be validated. One of the ways our team of clinicians and engineers achieves this is by analyzing precisely controlled experimental test data obtained from a robotic spine testing system (Figure 3). The accuracy of a computer model’s predictions can be validated by comparing the prediction with a set of known data obtained through *in vivo* and *in vitro* tests. If the results are not comparable, changes are made to the material properties of the model.

The flexibility of computational modeling allows us to make changes rapidly. The effect of various design parameters, such as shape, size, location of placement and material properties, can be altered to determine an optimal design. The validation process is repeated until comparable results are obtained.

By using these sophisticated computational models, we hope to gain a better understanding of the interaction between the spine and various spinal implants. We are also expanding our research domain to include modeling of previously unstudied regions of the spine.

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**Figure 2. Computer spine models with various spinal implants (shown in red).**

**Figure 3. Robomechanical spine testing.**

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In recent months, Cleveland Clinic nurses in the Neurological Institute have implemented a number of innovative practices to improve the quality of care for hospitalized neurological patients. This article profiles three of these initiatives: (1) efforts to support earlier mobilization of patients in the neurological ICU, (2) a quest to identify a best-practice tool for measuring delirium in the same group of patients and (3) a new unit structure to give patients on the neurological medical-surgical unit greater consistency with respect to their caregivers.

An Early Mobility Protocol for the Neuro ICU

When Cleveland Clinic advanced practice nurses (APNs) set out to establish an early mobility protocol in the neurological ICU, they reviewed the literature for evidence-based practices and learned that critically ill patients with neurological injuries had largely been excluded from studies of early mobilization.

They found, however, that available research on early mobilization in other critically ill populations revealed several beneficial outcomes: reduced risk of hospital-acquired conditions such as pressure ulcers, decreased length of stay due to deconditioning, and reduced rehabilitation needs after discharge. Hypothesizing that early mobility would also benefit critically ill patients with neurological injury, the APN team created an early mobility protocol to accommodate patients in the neurological ICU.

After gaining support from ICU leaders and other ICU clinical nurse specialists, the team began investigating its hypothesis by implementing the early progressive mobility protocol in the neurological ICU on Cleveland Clinic’s main campus in late February 2012.

The protocol leads nurses to advance patients through increasing degrees of mobility as soon as approved by a physician. Criteria guide nurses on when to initiate and when to proceed to the next steps; exclusion criteria are also specified. Nurses use their clinical judgment and the patient’s response to mobility to advance through the protocol. Patients can thus make progress without needing to wait for a new order before moving to the next step. Further, bed features that promote early ambulation and a lift device are being assessed for usefulness in the mobilization process.

A designated nurse representative is temporarily assigned to a unit for several hours a day to encourage progression of mobility, help with documentation and assist with the physical aspects of mobility promotion.

The protocol has been complemented by other changes to the neurological ICU. More physical and occupational therapists have been added, and specially designed chairs have been introduced with features to make it easier to get patients out of bed regardless of their weight or physical handicaps. Unit nurses were trained by physical and occupational therapists to use the chairs and mobility bed features and were offered additional instruction in body mechanics.

Seeking the Best Tool to Monitor for Delirium

Cleveland Clinic nurses also are currently investigating which of three methods of assessing delirium — the Confusion Assessment Method for the ICU (CAM-ICU), the Intensive Care Delirium Screening Checklist or the neurointensivist’s subjective impression — represents best practice for evaluating delirium in patients treated in the neurological ICU.

Delirium is important to identify because it can be an early sign of worsening primary injury, a sign of new-onset secondary injury, a form of evolving metabolic derangement or a psychological problem. Early identification is particularly important because the longer patients remain in a state of delirium, the more likely they are to have other complications of care and poor long-term outcomes.

Delirium affects 30 to 80 percent of ICU patients and is a major driver of ICU costs. Despite being a neurological condition, delirium is not traditionally monitored in neurological ICUs even though it is widely assessed in other critical care settings. Because delirium symptoms closely resemble those of many potentially lethal neurological conditions — including vasospasm, cerebral edema, meningitis and encephalopathy — there has been concern that misdiagnosing symptoms as delirium early on could mean missing or mistreating these life-threatening conditions.

Delirium is not traditionally monitored in neurological ICUs even though it is widely assessed in other critical care settings.
Until a best-practice delirium instrument is identified for use based on results from their ongoing research, Cleveland Clinic nurses are focusing on what they can do at the bedside to mitigate suspected delirium in their patients. The best treatment for delirium is to find and treat the underlying cause. If neurological injury and metabolic derangement have been ruled out, the best treatment for delirium involves simply normalizing the patient’s day by frequent orientation to surroundings, date and time. Also, getting patients moving as early as possible, having them sit in a chair so they can better interact during family visits, and facing them toward the window so they can see if it is day or night can help promote clear, organized thinking.

Increasing Consistency in Caregivers to Improve Patient Experience

The 50-bed neurological medical-surgical unit on Cleveland Clinic’s main campus is a busy crossroads of patients with various diagnoses requiring differing levels of care. Fifteen to 20 discharges and admissions are not uncommon on the unit in a single day. The average length of stay is three to four days, during which time patients can interact with many different caregivers.

Cleveland Clinic nurses recognized that these factors could hinder patients’ and their families’ ability to process information and have a positive experience in the hospital. They thought it was important to provide a more intimate and patient-centered experience. So, in the middle of 2011, in a joint effort with Neurological Institute physicians, care managers and therapists, nurses set out to find a way to provide more consistency in the caregivers a patient interacts with in this environment.

The pods are virtual, not physical, as patients in the same pod are not necessarily located next to one another on the unit. The volume and movement of patients through the unit would make it too time-consuming to continually relocate patients to accommodate proximity-based pods.

Each pod is overseen by a midlevel provider. Cleveland Clinic has hired a total of eight APNs and physician assistants into these new positions. Each midlevel provider works with the attending physician and resident and is on the unit daily, interacting with patients in his or her pod several times a day. Case managers and physical therapists, previously assigned by unit, are now also assigned to pods, thereby providing a stable team environment, better coordination and enhanced communication among caregivers. Patients benefit from the consistency of seeing the same group of caregivers throughout their hospital stay.

Because nurses have greater shift variability and need to balance varying degrees of physical demands from patients, it was particularly challenging to attempt to assign nurses to pods. Nurses also expressed a desire to continue to work with a variety of patients in order to keep up their skills. For these reasons, the decision was made to not assign nurses (other than the APN midlevel providers mentioned above) to pods.

Nurse and physician leaders meet regularly with the midlevel providers, case managers and nursing staff to discuss the new pod structure and find ways to improve it. The group has begun quarterly reviews of patient satisfaction scores related to the new structure. Current data are preliminary, but some areas are showing improvement in scores.

Each midlevel provider interacts with the patients in his or her pod several times a day.

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Cleveland Clinic Gamma Knife Center
Cleveland Clinic main campus
Cleveland, Ohio

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Sixth Annual International Symposium on Stereotactic Body Radiation Therapy and Stereotactic Radiosurgery
Course Directors: Lilyana Angelov, MD; Sam Chao, MD; Gene Barnett, MD; Edward Benzel, MD; and John Suh, MD
Disney’s Grand Floridian Hotel and Resort
Lake Buena Vista, Fla.

APRIL 6, 2013
Third Annual “Parkinson’s and Its Look-Alikes” Symposium
Course Director: Hubert Fernandez, MD
Marriott Key Center Hotel, Downtown Cleveland
Cleveland, Ohio

APRIL 17-19, 2013
2013 Sleep Symposium — Wake Up to Sleep Disorders
Course Directors: Nancy Foldvary-Schaefer, DO, and Tina Waters, MD
Embassy Suites Hotel
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JUNE 21, 2013
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Course Director: Alex Rae-Grant, MD
InterContinental Hotel & Conference Center
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Lutheran Hospital
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AUGUST 2-4, 2013
2013 Neurology Update — A Comprehensive Review for the Clinician
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The Ritz-Carlton Hotel
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