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On the cover: High-magnification photomicrograph of the GAP-43 immunocytochemical staining of an epileptic/dysplastic cortex.
Dear Colleagues,

As the practice of medicine evolves to ever-higher levels of complexity, driven by relentless forces such as specialization, technological progress, and our inherent need to understand and conquer disease, we are constantly reminded of how interdependent we are as healers. None of us, no matter how gifted, can be all things to our patients. Successful collaboration is not optional; for patients, it can tip the scales from preventable death to resumption of a functional, satisfying life.

Cleveland Clinic Neurological Institute was founded on the premise that medical specialists, surgeons, nurses, research scientists, residents and allied healthcare professionals who are trained in the treatment of nervous system disorders belong together in a collaborative environment with a disease-specific focus. This approach manifests each morning at our main campus Huddle, where the institute staff gathers to review the status of individual inpatients and discuss the plan of care. Within the institute’s centers, this integrated structure links diverse teams of medical and surgical specialists in regularly scheduled patient management conferences that include participants in remote locations such as Cleveland Clinic Florida.

Grouping neurological caregivers in one multidisciplinary unit was the first step toward integration on a broader plane, our current focus. Specialists in stroke care, sleep disorders, epilepsy, movement disorders, neuroimaging, brain health and post-acute care now partner in research studies and utilize common clinical protocols that span geographic divides. In this issue of Pathways, for example, we describe the carepath that guides management of all stroke patients from the moment they present through their post-discharge care.

Another model of clinical integration can be found in post-acute care, where Frederick Frost, MD, Interim Director of our Department of Physical Medicine and Rehabilitation, and Steven Landers, MD, MPH, Director of Cleveland Clinic at Home, are structuring a continuum to effect seamless transitions between levels of care, from hospital to home.

A key component of this spectrum is home-based rehabilitation. This issue reports on Cleveland Clinic at Home’s program after total knee arthroplasty, which draws on the complementary strengths of the Orthopaedic & Rheumatologic Institute and the Neurological Institute. This and similar innovations, such as our Heart Care at Home program, are creative responses to a rapidly changing environment in which patients increasingly aspire to return to their homes as quickly as possible and remain there as long as feasible. A team approach is fundamental to managing their expectations and needs — and to assuring them that when they leave a Cleveland Clinic hospital, Cleveland Clinic does not leave them.

This publication integrates additional examples of teamwork and innovation throughout the Neurological Institute, in the laboratory and at the bedside. We invite you to read on, and we welcome any opportunity to collaborate with you.

Sincerely,

Michael T. Modic, MD, FACR
Chairman, Cleveland Clinic Neurological Institute
Uncovering the Molecular Mechanisms of Epileptogenesis in Malformations of Cortical Development

By Imad M. Najm, MD, and Zhong Ying, MD, PhD

Malformations of cortical development (MCD) are recognized as common pathologic substrates in patients with medically intractable epilepsy, where the first seizure may occur at any point and at any age. In most patients, the initial seizure can be provoked by a “second-hit” brain insult such as minor head trauma, brain infection or cerebral ischemia. Following a latent period after the second hit, seizures become more difficult to control with anticonvulsants.

Epilepsy is characterized by the occurrence of bursts of paroxysmal neuronal activities and high episodic synchronization. The intrinsic neuronal cell membrane properties such as ion channels and postsynaptic glutamate receptors determine neuronal excitability, whereas local axonal network reorganization contributes in part to increased synchronization.

At Cleveland Clinic Epilepsy Center, we aim to understand the molecular/cellular changes that underlie the development of the excitatory networks during the latent period following the second hit in patients who harbor MCDs and in a rat model of in utero radiation-induced diffuse cortical dysplasia.

Epileptogenesis in a Rat Model of Cortical Dysplasia

Using a rat model of radiation-induced cortical dysplasia, we showed that a second hit — a single, low, subconvulsive dose of pentylenetetrazole (PTZ) — in rats with in utero-induced cortical dysplasia that did not develop spontaneous ictal patterns renders the majority of dysplastic rats (but not age-matched control animals) epileptic.

These findings mirror part of the natural history of a significant number of patients with MCD (thought to be due to prenatal/congenital or perinatal insults) in whom the epileptic phenotype does not develop until an otherwise nonepileptic stressor (such as trauma, acute infection, stress, sleep deprivation) transforms a nonepileptic pathology into an epileptic phenotype.

In order to understand the gene mechanisms of epileptogenesis, we performed a gene expression analysis of the in utero irradiation-induced dysplasia in the rat model. The gene expression analysis revealed some of the potential mechanisms by which MCD may result in an intractable epilepsy phenotype:

- Downregulation of genes involved in glutamate and AMPA receptor recycling may lead to increased excitability.
- Downregulation of the gene Shank-1 may lead to disinhibition of aberrant dendritic branching, resulting in an increase in sprouting, excitation and/or hypersynchrony.
- Increased expression of genes promoting cell survival, either directly (connective tissue growth factor, peroxiredoxin) or indirectly (latrophilin-2), may allow MCD tissue to survive the excitotoxic injury that it produces, perpetuating the epileptic condition over time.

One synaptic marker used to investigate axonal sprouting is growth-associated protein-43 (GAP-43), a neuronal presynaptic membrane-bound protein that is maximally expressed during neuronal development to initiate axonal outgrowth and synaptic formation. Once growing axons reach their targets and synaptogenesis is established, GAP-43 levels rapidly decline. Re-expression (upregulation) of GAP-43 proteins in the mature brain occurs during attempted pathologic aberrant axonal regeneration such as mossy fiber sprouting in the hippocampal synaptic plasticity of human mesial temporal lobe epilepsy. GAP-43 has also been shown to be involved in the plasticity of adult neurons in the neocortex after brain insults such as ischemic stroke and traumatic brain injury.

To further investigate the role of second-hit brain insults in triggering the aberrant axonal network formation in cortical dysplasia (MCD), we investigated the expression of GAP-43 in an adult rat model of radiation-induced MCD by administering a single subconvulsive dose injection of PTZ to provoke seizures. Our most recent data showed that GAP-43 proteins increased in the brains of rats with MCD brought on by in utero-induced radiation (but not in control brains) following a single seizure.

Molecular Mechanisms of Epileptogenesis in Human MCD

Because GAP-43 is recognized as having a significant functional role in axonal growth and sprouting that may account for one of the epileptogenic mechanisms in MCDs, we investigated the expression patterns and levels of GAP-43 protein in human epileptic MCD specimens surgically resected from patients with medically intractable focal epilepsy. The surgically resected nonepileptic and epileptic cortical regions were studied. Areas of ictal onset and frequent interictal epileptiform discharges were defined through extraoperative or intraoperative electrocorticographic recordings.

Because expression of GAP-43 protein can be induced by physiological activities such as learning and memory and due to the well-known facts of axonal sprouting from mesial temporal structures to the orbital-frontal cortex via the uncinate fasciculus, we excluded specimens from temporal or orbital-frontal lobes from the study. We also examined the corresponding expression of phosphorylated neurofilament proteins, which are widely distributed in the neuronal axons. We conducted immunohistochemistry with GAP-43 antibody to examine the cellular expression patterns of GAP-43 protein. Our results showed that,
compared to normal-appearing cortical specimens resected from the same patients, GAP-43 protein stainings were increased in the MCD specimens. Furthermore, as shown in Figure 1, the increased GAP-43 proteins in the MCD cortex were distributed in the tubular structures that may represent sprouted and disorganized axonal connections. In parallel, we also found that in the same MCD region where GAP-43 proteins were increased, there was a corresponding increase of axonal neurofilament proteins identified through immunohistochemistry with anti-SMI-312 antibody (Figure 2). To further test the hypothesis that aberrant axonal sprouting and reorganization may contribute to the epileptogenic mechanisms, we used Western blot to semi-quantify the levels of GAP-43 presynaptic proteins in paired tissue samples within the same patients: epileptic vs. nonepileptic tissues.

If confirmed in a larger number of samples from human and animal models of MCD, this preliminary finding suggests that MCD may have the intrinsic capability of developing an epileptic synaptic network by aberrant axonal sprouting triggered by the second-hit brain insult.

These results suggest that the in situ expression of GAP-43 proteins can be identified as the targets for future innovative medical therapeutics. Development of new medications or interventions designed to block the expression of GAP-43 proteins can provide alternative treatment options to prevent epileptogenesis in MCD patients.

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Identifying Depression in Epilepsy Patients for Better Outcomes

By George E. Tesar, MD

At Cleveland Clinic, physicians treating patients with epilepsy regularly utilize the Neurological Institute’s Knowledge Program® (KP) to assess psychiatric comorbidities commonly associated with epilepsy. Depressive disorders are the most common. Routine depression screening and serial measurement of depression provide valuable data toward understanding depression’s relationship with epilepsy and optimal treatment, promoting better overall outcomes.

In 400 B.C., Hippocrates wrote “On the Sacred Disease,” a paper exploring what is now known as epilepsy. Physicians once believed the disorder was spiritual or demonic in nature — divine or evil beings fought over a person’s soul, causing the seizures and visions. Modern doctors certainly have a better understanding of epilepsy, yet a few mysteries still cloak the disease. One of these present enigmas concerns the comorbidity of epilepsy and depression.

Hippocrates also recognized the coexistence of the two disorders. A number of common psychiatric disorders prevalent in the general population (e.g., anxiety, attention deficit/hyperactivity and psychoses) are four to five times more common in patients with epilepsy, with published rates of depression from 20 to 50 percent.

Despite these findings, depression often goes undetected and untreated. Time factors, focus on the epilepsy and patient reluctance to identify depression as a problem contribute. The treatment of depression in primary care has been studied extensively, and because it has been well-established that detection of depression does not by itself improve treatment outcome, care services must be designed to facilitate treatment. The KP, which is focused on detection and serial measurement of outcomes, is therefore a necessary first step (although insufficient by itself) in tackling this problem in patients with epilepsy.

In 2007, the Epilepsy Center was among the first of the Neurological Institute’s 18 centers to start collecting KP data. The process involves data collection — most of it by the patients — at the point of care. When checking in for an appointment, the patient is asked to complete center-specific questionnaires. Responses are entered by the patient or an assistant on a touch-screen tablet computer. The tablet is then returned to desk personnel for uploading of the collected data so it can be viewed in Epic, Cleveland Clinic’s electronic medical record, allowing the patient’s clinician access to survey responses during the clinical encounter.

Each center selects survey instruments specific to the needs of its patients. All Neurological Institute patients, including those of the Epilepsy Center, complete two questionnaires: the European Quality of Life Five Dimensions short form and the Patient Health Questionnaire-9 (PHQ-9), a diagnostic scale ranked from 0 to 27 that assesses the presence and severity of depression symptoms. Used extensively in primary care, the scale is designed to detect major depressive disorder (MDD) as defined in the Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association. Scores of 10 or higher have been shown to correlate with MDD. In the Epilepsy Center, patients complete a number of other survey instruments, including the Liverpool Seizure Severity Scale and the Quality of life in Epilepsy Scale, a 10-point scale evaluating overall satisfaction with life.

Recently, we performed a retrospective review of these data in a sample of 2,015 patients who made 5,732 visits to the Epilepsy Center from Jan. 1, 2009, to Dec. 31, 2009. Seventy percent accounted for one or more visits, with 2 percent attending eight or more appointments. The analysis included demographic data as well as driving status, epilepsy type (focal, generalized or undefined), number of anti-epileptic drugs and antidepressant medication use.

Four hundred seventy-six patients (23.6 percent) suffered from at least a moderate degree of self-rated depression: 246 (12.2 percent) rated their depressive symptoms as moderate, 142 (7 percent) as moderate/severe and 88 (4.4 percent) as severe. According to the National Institute of Mental Health, the 12-month prevalence of depression in the adult general population is 6.7 percent, with a mean lifetime prevalence of 16.5 percent.

Predictors of clinically significant depression included older age, African-American race, being single, and being unable to work or drive. These data were presented at the 64th Annual Meeting of the American Epilepsy Society in San Antonio, Texas, Dec. 4, 2010, and are in preparation for publication.
As far as we know, this is the largest study of depression detection in epilepsy patients using a highly efficient, clinically relevant survey tool. Our results focus on the importance of detection as a first step. Because some patients are offended by the “depression” label, it is imperative that doctors approach any discussion of the problem sensitively. Epileptologists have become increasingly sophisticated in their detection and management of depression, because more attention has been devoted to it in the literature and here at Cleveland Clinic. The problems already cited that interfere with optimal management have encouraged us to develop strategies promoting seamless integration of epilepsy and psychiatric services. Plans are under way to increase trainee exposure to and involvement in this exciting example of integrated healthcare.

The mean PHQ-9 score improved from 7.9 (± 0.3) at the initial visit to 6.0 (± 0.3) at the last follow-up visit, reflecting a 25 percent reduction in depression score severity (P < 0.0001). The standard box plots reflect the median and the 25th and 75th quartiles. N = adult epilepsy patients treated with medications only and with greater than six months of follow-up. Mean duration of follow-up was 12.4 months.

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Immunotherapy: A New Therapeutic Approach to Treating Alzheimer’s Disease

By Jeffrey Cummings, MD, ScD, and Xue (Kate) Zhong, MD, MSc

With the incidence of Alzheimer’s disease (AD) estimated to increase dramatically in the coming decades, more effective therapeutic agents are urgently needed. Cleveland Clinic Lou Ruvo Center for Brain Health is actively investigating a number of therapeutic approaches, including immunotherapy, which has recently gained considerable attention. Studies have shown that immunotherapy can improve brain health and cognitive function in animal models and may represent treatments for AD patients.

Alzheimer’s disease is a neurodegenerative disease characterized by progressive memory deficits, cognitive impairment and personality changes, and is eventually fatal. It is the most common cause of dementia in the elderly, affecting approximately 18 million people worldwide; in the United States, approximately 5 million people have AD.

Age is the major risk factor for AD. Its prevalence increases with age: from approximately one in 100 people over 60 to approximately one in three people over 85. AD-related complications are a major cause of death in the elderly population. As the population of people over 65 grows in the coming decades, the U.S. AD population is estimated to increase to 7.7 million by 2030 and 14 million by 2050. This will place an enormous burden on the healthcare system and on the family members, caregivers and medical professionals who care for AD patients.

Existing therapeutic options, which include cholinesterase inhibitors such as donepezil, rivastigmine and memantine, focus on modifications of neurotransmitter systems to maximize the remaining activity in neuronal circuits damaged by the disease. However, there are currently no treatments that address the underlying disease process or slow disease progression.

Targeting AD Pathology With Immunotherapy

AD is characterized by the abnormal accumulation of amyloid plaques in the brain. The predominant component of these plaques is beta-amyloid protein (Aβ), particularly a 42-amino acid isoform (Aβ 1-42) that is derived from a larger amyloid precursor protein. Over the past decade, beta-amyloid has become a major therapeutic target.

Immunotherapy has emerged as a potentially promising therapeutic approach to decrease production and promote clearance of Aβ in the brains of AD patients. In studies of animal models and human subjects with AD, active and passive immunization has been shown to reduce cerebral Aβ levels.

In the first study of Aβ immunotherapy, active immunization with aggregated Aβ 1-42 lowered cerebral Aβ levels and improved cognitive function in platelet-derived growth factor promoter driven amyloid precursor protein (PDAPP) mice, an animal model of early onset familial AD. Unfortunately, in a 2002 clinical trial of active Aβ 1-42 immunization of AD patients, approximately 6 percent of subjects developed meningoencephalitis. It may be that full-length Aβ 1-42 was recognized as a self-antigen, leading to an autoimmune response in some patients. Subsequently, new immunogens have been formulated that target Aβ epitopes and avoid Aβ-specific T-cell reactions.

In a study of passive immunotherapy with intravenous immunoglobulin (IV Ig), the treatment was well-tolerated by eight mild-AD patients who had decreased levels of Aβ in cerebrospinal fluid and showed cognitive improvement as measured by an increase in Mini-Mental State Examination scores. Bapineuzumab, a monoclonal anti-Aβ passive immunotherapy, has been shown to reduce brain plaques in humans assessed with amyloid brain imaging.

Another AD therapeutic target is the tau protein, which accumulates in nerve cells as tangles. Since the tau protein is most closely associated with AD nerve cell death, reducing tau protein could have a major impact on disease progression. Immunotherapy targeting tau protein has been studied in animal models but not yet in human subjects.

Immunotherapy Trials at Cleveland Clinic

Lou Ruvo Center for Brain Health is building a comprehensive AD trial program at Cleveland Clinic centers in Las Vegas, Cleveland and Florida. Eleven trials are under way evaluating various AD therapeutic agents. Four trials involve active and passive Aβ immunotherapy; two are focused on patients in the prodromal phase of AD, when treatment can have a greater impact on disease progression.

Studying the prodromal AD population is an important new direction in AD clinical trials, made possible by advances in AD biomarkers. Cerebrospinal fluid tests can measure the levels of beta-amyloid and tau protein, with levels of beta-amyloid decreased and levels of tau protein increased in AD patients. PET imaging used with the radioactive tracer Avid-45 (18F-AV-45 PET) can detect deposits of amyloid protein, which may appear long before AD becomes symptomatic.
Two trials are evaluating ACC-001, a conjugate of approximately 15 peptides of Aβ1-7 conjugated to cross-reactive material (CRM197), a nontoxic variant of diphtheria toxin that has been used effectively as a carrier protein for several glycoconjugate vaccines. In one trial, subjects aged 50 to 89 with prodromal or mild-to-moderate AD will receive six intramuscular doses of ACC-001 over a 24-month period.

In another trial, passive immunization with IV Ig is being evaluated over 18 months in subjects aged 50 to 89 with mild-to-moderate AD. Participants receive an infusion of IV Ig every two weeks for 72 weeks. The primary biomarker for the studies is the change in cerebral amyloid burden as measured by 18F-AV-45 PET. Immunogenicity will be measured by a serum anti-Aβ immunoglobulin G (IgG) titer assay. Subjects will also undergo cognitive and neuropsychological testing.

Another is a Phase II randomized, double-blind, parallel-group, placebo-controlled study to evaluate the effects of MABT5102A on brain amyloid burden (as assessed by flortbetapir-PET) and other biomarkers in patients with mild-to-moderate AD. In this 68-week study, patients will first receive the treatment subcutaneously every two weeks, followed by IV infusion every four weeks. MABT5102A is a fully humanized IgG4 monoclonal antibody to Aβ, selected for its ability to bind both monomeric and oligomeric forms of Aβ in vitro.

**Clinical Trials: The Pathway to New Treatments**

If the treatments evaluated in the trials show convincing results, they will be submitted for FDA approval. Clinical trials that show efficacy of treatment by comparison with a placebo are the only way to gain FDA approval for new therapeutic agents and are critical to the development of effective treatments for AD. Trials are in constant need of participants, who receive comprehensive medical care and are carefully monitored throughout the trial. We encourage neurologists to discuss participating in AD trials with their patients with prodromal or mild-to-moderate AD. Feedback from trial participants has been very positive; they feel empowered by contributing to the development of new AD treatments that can potentially help others with the disease.

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**REFERENCES**


Angiogenesis in Malignant Brain Tumors

By Candece L. Gladson, MD

The growth of new blood vessels, a process called angiogenesis, is thought to be necessary for the growth of malignant tumors, including malignant brain tumors. Consequently, it is considered a prime therapeutic target, but the design of effective therapies requires an improved understanding of what contributes to the development of the tumor-associated angiogenesis and its subsequent regulation.

During normal processes such as wound healing, new blood vessels develop from existing blood vessels in a process that is self-limiting, so that new blood vessels ultimately mature and stop growing. New blood vessels associated with tumors clearly differ; they are structurally abnormal, frequently leak, fail to mature completely and are continually growing. In fact, tumor cells can promote new blood vessel growth by creating an environment that mimics the normal physiological process. It is now apparent that tumor-associated angiogenesis may differ fundamentally from “normal” vessel growth because the endothelial cells that line blood vessels can arise not only from existing blood vessels but also from cancer stem cells.

Likely therapeutic targets are those molecules that determine the fate of the endothelial cells. These molecules govern apoptosis — the regulated or controlled life and death of cells — and might provide a way to either trigger or inhibit new blood vessel growth.

Two-Pronged Research Into Tumor-Associated Angiogenesis

One goal of our research is to identify and explain how new blood vessel growth develops and is sustained in malignant brain tumors, particularly the highest grade of malignant glioma, called glioblastoma. In other words, how do molecular events in brain tumor-associated angiogenesis differ from “normal” blood vessel growth?

A second focus of our research is to identify those molecules or mechanisms that inhibit the survival of brain endothelial cells, thus actually promoting cell death. Knowing how they elicit cell death could be a potential therapy for controlling or inhibiting tumor-associated blood vessel growth.

In short, there may be two separate “switches” for tumor-associated angiogenesis — one that turns on vessel growth and another that inhibits it. Regulation of tumor-associated angiogenesis may require “flipping,” or turning on, the inhibitory switch in a specific time frame relative to the turning on of new blood vessel growth.

During the last two decades, there has been much work in the development of new therapies that would target vascular endothelial growth factor (VEGF), a potent protein that spurs angiogenesis and that is synthesized by tumor cells and some stromal cells. Several studies have shown that targeting of VEGF has a short-term beneficial effect in some glioblastoma patients. However, this new therapy does not improve overall survival for patients with glioblastoma. Furthermore, in mouse models of cancer, antibody therapy directed toward VEGF can result in a change in the physical and biochemical characteristics of the tumor and the development of a more aggressive and invasive tumor.

Remaining Gaps in Knowledge of Angiogenesis and Anti-Angiogenic Therapy

Anti-angiogenesis strategies show promise in the treatment of malignant gliomas. However, it is evident that more information is needed if this promise is to be realized. In common with most cancer therapies, anti-angiogenic therapy in general is limited by the tumor's ability to change its physical and biochemical characteristics. This issue is being addressed through two primary efforts. The first is to explain how tumors develop resistance to specific anti-angiogenic therapies. The second is to develop therapeutic strategies that target cancer stem cells, pro-survival proteins and as-yet-unidentified proteins that regulate angiogenesis — new strategies that can be used either in combination with other anti-angiogenic therapies or other types of therapy to eliminate tumor development or, more likely, as alternative therapeutic strategies in tumors that have become resistant to the initial therapy.
There are three requirements for optimal clinical application of anti-angiogenic therapies. First, we must identify the preliminary indicators of a positive or negative response to anti-angiogenic therapy in general, as well as to specific anti-angiogenic therapies. Second, we must identify the class or type of chemotherapeutic agent that provides optimal responses in combination with anti-angiogenic therapy. Finally, we need to identify the biomarkers of angiogenesis that can be used to monitor the response to anti-angiogenic agents and to detect tumor recurrence.

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Tumor angiogenesis in a glioblastoma biopsy. A formalin-fixed and paraffin-embedded section of a glioblastoma tumor biopsy was reacted with an endothelial cell-specific antibody directed toward von Willebrand factor, followed by a horseradish peroxidase-labeled secondary antibody and the diaminobenzidine substrate (gives a brown color where antibody reactivity occurs) and then counterstained with hematoxylin. The arrows indicate the abnormal blood vessels typically found in glioblastoma tumors.
The Knowledge Program and Carepath: Hints at a Revolution in Healthcare Delivery

By Irene Katzan, MD, MS

The Knowledge Program® at Cleveland Clinic Neurological Institute is much more than a database for the care of neurological patients. It is the basis of a shared decision-making model that the Neurological Institute calls a “carepath” — and is opening a new frontier for data-driven but personalized and patient-centered treatment of disorders that is applicable to any discipline of medicine.

The Knowledge Program is based on the premise that measurement is needed to evaluate the efficacy of any medical decision or process. Accurate assessment of patient outcomes and the effectiveness of management is difficult, if not impossible, without data. Yet obtaining clinical data can be a challenge, and available data stores are often disorganized and restricted in scope and offer limited access, thus hampering their meaningful use.

Data is the Knowledge Program’s foundation — electronic clinical information gathered as part of clinical encounters. The two main data categories are:

- The contents of self-administered electronic questionnaires that patients complete before each clinical visit. The questionnaires measure patients’ health status based on standardized questions — both generic and disease-specific — that address individual patients’ perceived health. The data sets now reflect more than 400,000 clinical visits by more than 150,000 unique patients, and the number of captured encounters grows by 18,000 per month.
- Other clinical data extracted from our Epic Systems EHR platform and other data repositories, such as laboratory tests, imaging results, medications and many other variables.

A sophisticated but easy-to-use query tool permits convenient access to data that can be used for multiple types of analyses. This tool is a way to research the comparative effectiveness of treatment options based on outcomes relevant to the patient. The query tool is web-based, so authorized users can analyze data from any Internet-connected computer.

Next Steps: Carepaths

With these new data, and a new capacity to explore them, we are moving toward a new clinical care paradigm: the carepath. Carepaths utilize comprehensive care protocols developed by clinical experts that are tightly incorporated into the electronic health record, ensuring a systematic approach to management for all patients. They can incorporate reminders and outcome prediction tools that allow real-time treatment adjustments. The concept was first tested in the medical condition of stroke — a leading cause of long-term disability and the most common neurological reason for hospital admission. In the first nine months of implementation, over 500 patients have been managed with the assistance of the carepaths.

The integration of clinical protocols directly within the clinical workflow of the EHR, coupled with systematic collection of patient-reported health status information, helps optimize stroke patient care and ensure that the provider meets standards of care at every stage of care for every patient.

More Variables, but More Precision

The range of variables available to help us in patient management and research is much broader and richer because of the clinical information entered discretely by the provider and the health status data completed by the patients in the stroke carepath. These validated health status measures document outcomes that are relevant to the patient and provide much more useful and specific information than do the more standard outcomes of mortality or readmission.

For instance, examination of a patient might indicate to stroke care providers that they could restore flow in a blocked blood vessel. But would the restored blood flow actually improve a patient’s quality of life, or would it amount to an extraneous procedure? Evaluation of data from the Knowledge Program’s immense data store could predict the answer, based on outcomes from similar cases.
Red Flags and Reminders

Another feature of the carepath is that it actively informs and improves patient care in real time. The carepath infrastructure is designed to provide automated reminders to adhere to established, outcome-improving standard-of-care protocols. For instance, a prepopulated discharge checklist reminds a treating physician to consider placing stroke patients on a cholesterol medication at discharge.

Conventional quality control practices require an abstractor to manually pore over patients’ electronic charts, often two to three months after discharge. With the carepath system, real-time warnings allow us to address problems immediately. The warning systems included in the stroke carepath reduce retrospective chart review labor, time and expense so that resources can be redirected toward improving patient care.

Our plan is to take the Knowledge Program across medical boundaries and use it not just in stroke care but in all medical specialties.
We have also established mechanisms to schedule a follow-up visit 30 days after discharge for every stroke patient, regardless of insurance status or ability to pay. Those who cannot visit are contacted by phone. It is important to follow patients through the early period after discharge, a sensitive time when problems can arise. In addition, the integrity and applicability of our data depend on collecting 30-day outcomes from as many patients as possible — including those who feel too sick to return or who live far away.

**Stroke Care and Beyond**

In the Knowledge Program’s first three years, we accomplished our initial goals. We established an infrastructure to systematically collect patient-centered health status information, use it to help optimize management, and make it accessible for research and quality. We created and implemented the carepath model and established methods to monitor patients after discharge and evaluate 30-day outcomes. We are continuing to move forward. The electronic infrastructure developed for stroke care is a template that will be adapted to many different types of diseases. Our plan is to take the Knowledge Program across medical boundaries and use it not just in neurosciences but in all medical specialties.

The Knowledge Program strategy, broadened beyond neurology and the walls of Cleveland Clinic, may transfigure the way we apply data, conduct comparative research, identify the most effective strategies and reduce extraneous care. It may be one of the solutions for health-care reform we have all been seeking.

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Acute Ischemic Stroke

When time is of the essence, Cleveland Clinic Critical Care Transport can bring the critically ill to our 24/7, in-house, neuro-intensivist-staffed Neurological Intensive Care Unit.

By Ferdinand K. Hui, MD

Presentation
A woman in her 70s was hospitalized for atrial flutter, a condition in which her heart was beating irregularly. In the hospital, she suddenly experienced left-sided weakness, difficulty speaking, left arm paralysis, leg weakness, limb ataxia, neglect and sensory loss. Computed tomography angiography showed a clot in the right middle cerebral artery (MCA). Rapid administration of intravenous r-tPA and transfer via Cleveland Clinic Critical Care Transport (CCT) immediately followed.

Examination
Upon arrival at our neuro-intensivist-staffed Neurological Intensive Care Unit, her stroke symptoms had worsened, gaining another point on the NIH Stroke Scale (NIHSS), now with a score of 14. Hyperacute MRI was performed, showing acute ischemic changes in the right caudate nucleus, the right lentiform nuclei and the right frontal corona radiate. Given her score, the large clot in her right middle cerebral artery and the apparently small area of permanently injured brain, the decision was made to bring her to the angiography suite for mechanical thrombolysis and thrombectomy.

Treatment
The patient was brought to the angiography suite under conscious sedation. The neuro-interventional team rapidly deployed an aspiration catheter and thrombectomy device into the right MCA, disrupting and removing the clot. Blood flow was restored to the portion of the right brain supplied by the right MCA in under five minutes of aspiration.

The day after the procedure, when the patient had recovered from sedation, her neurological exam had improved markedly, with mild residual difficulty speaking, mild-to-moderate left arm weakness and mild-to-moderate left facial weakness. With a total NIH Stroke Scale score of 5, she was discharged to a rehabilitation facility.

Outcome and Follow-Up
On follow-up at six weeks, the patient’s score was reduced to 3, with mild dysarthria, left arm drift and slight residual facial weakness. She has made a remarkable recovery.

Conclusion
When a brain is dying during an acute ischemic stroke, time is of the essence. Life- and brain-saving techniques can be employed only while the brain tissue is still viable. With every second, more brain cells die. Without a system like Cleveland Clinic Critical Care Transport, getting this patient to a 24/7, in-house facility with state-of-the-art techniques and equipment in time might not have been possible. The autolaunch protocol allows the transport service to be en route even as the patient’s specific case is being discussed, saving precious time and precious brain matter.

Our critical care transport is a portable version of Cleveland Clinic’s neurological intensive care unit. This means our skilled CCT team members deliver the first line of therapy, which is aggressive medical management, stabilizing the patient for transport to Cleveland Clinic for definitive interventional therapy. While this particular patient was from Northeast Ohio, our entire critical care transport system is about having the means and resources to bring Cleveland Clinic’s expertise and reputation to the patient’s bedside anytime and anywhere in the world — with the goal of improving quality of life for critical care patients.
The value of high-performing post-acute care is becoming apparent as healthcare reform turns hospital readmissions into a top-of-mind issue. The Medicare Payment Advisory Commission (MedPAC) has identified the readmission rate as an outcome measure that provides “an integrated assessment of quality because it reflects the result of multiple care processes provided by all healthcare providers involved in the patient’s care.”1 Additionally, the assessment of readmission rate focuses “attention on much needed system-level improvements, because achieving the best patient outcomes often requires carefully designed care processes, teamwork, and coordinated action on the part of many providers.”1

A variety of proposals aimed at holding hospitals and physicians accountable for thorough and appropriate patient care beyond their doors has been advanced. Citing data that shows that many hospital readmissions are preventable, these rates will very likely serve as a yardstick under a system of “value-based purchasing” (VBP), wherein providers whose risk-adjusted 30-day readmission rates compare favorably with strong performers will receive higher reimbursement rates. According to MedPAC, the efficient providers have readmission rates 1 to 5 percent lower than the national average.1

Experts note that the data suggesting many readmissions are preventable is strong and that up to 20 percent of Medicare patients are readmitted to the hospital within 30 days of discharge.2,3 Most agree that sweeping reform measures will ultimately pass, and hospitals will be subject to financial penalties for poor performance in this area. Readmission rates may become the carrot or the stick, depending on efforts to improve care transitions across settings, identify risk and prevent avoidable readmissions.

Cleveland Clinic at Home has demonstrated significantly lower all-cause Medicare beneficiary acute hospitalizations than both the state of Ohio and national averages for all populations served (Figure 1).

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Cleveland Clinic at Home has demonstrated significantly lower all-cause Medicare beneficiary acute hospitalizations than both the state of Ohio and national averages for all populations served (Figure 1).

One important strategy discussed involves efforts to integrate acute hospital services with post-acute care through increased awareness of the patient’s experience from the point of admission to the completion of follow-up. This means closing any gaps in care that can lead to suboptimal outcomes, including readmission.

Cleveland Clinic at Home is collaborating with colleagues in the Heart & Vascular Institute (HVI), Neurological Institute (NI) and Orthopaedic & Rheumatologic Institute (ORI) to establish transitional care programs, including integrated care protocols, for heart failure and acute myocardial infarction (HVI), stroke care and falls-balance (NI), and total joint arthroplasty (ORI) patients. Our longest-standing integration effort has been with the Orthopaedic & Rheumatologic Institute for care of total joint arthroplasty patients (TJA). Engaged surgeons, coordinated carepaths and team communication have resulted in shorter acute lengths of stay and an increased number of patients discharged directly home following the acute inpatient stay. Acute hospitalization rates for Medicare beneficiaries receiving home healthcare from Cleveland Clinic at Home are well below reported national levels (Figure 2).
Five major forces may be cited for driving healthcare into the home: the aging of the U.S. population, epidemics of chronic diseases, technological advances, healthcare consumerism and rapidly escalating healthcare costs. Home healthcare will become a prominent care venue in the future. Continued development of innovative ways to care for patients is the path to desired outcomes and value for all stakeholders.

Cleveland Clinic at Home resides under the auspices of the Neurological Institute. Services provided at home include nursing care; specialized nursing services in behavioral health, wound-ostomy-continence management and diabetes education; home infusion therapy; respiratory therapy; physical, occupational and speech therapy; medical social work; and medical nutrition therapy consultation. Our Medical Care at Home division offers physician consultation, geriatric assessments, primary care services, palliative medicine consults and hospice services.

RECOMMENDED READING


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Renee Coughlin, PT, DPT, MHS, is Director of Rehabilitation Services at Cleveland Clinic at Home. Her specialty interests include geriatrics, evidence-based practice and the heart-brain connection’s impact on health. She can be contacted at 216.636.8618 or at coughlr@ccf.org.

REFERENCES

Risk Tolerance in Multiple Sclerosis Patients
By Robert J. Fox, MD

 Shortly after natalizumab (Tysabri®), an infusible medication for multiple sclerosis (MS), was introduced in 2004, concerns surfaced about serious side effects, including risk of progressive multifocal leukoencephalopathy (PML). Cleveland Clinic Mellen Center for Multiple Sclerosis Treatment and Research undertook a pilot study to evaluate the tolerance of MS patients to risks of therapy, particularly with natalizumab. Based upon this pilot study, a large-scale study funded by the National MS Society was conducted to further study tolerance to risk in more than 5,000 patients with the disease. The study also assessed the decision-making process MS patients used — where they sought information and what factors influenced their treatment choices.

Prior to the availability of natalizumab, medication choices for MS consisted of roughly four that were modestly effective and reasonably safe. Most of the decision to start therapy focused solely on whether the patient had active disease. If the answer was yes, treatment began with a beta interferon preparation or glatiramer (Copaxone®).

In 2004, natalizumab changed the landscape of MS therapy. In Phase III clinical studies, the drug reduced relapse rates by two-thirds (compared to one-third for the standard medications), reduced development of new brain lesions by more than 90 percent and slowed progression of disability by 42 percent. However, it was later found to carry a one in 1,000 risk of PML, with approximately 33 percent of people who develop it dying from the opportunistic brain infection.

After a 15-month hiatus from the market to evaluate the risk of PML, natalizumab was reintroduced in 2006. Since then, patients and clinicians have dealt with an increasingly complicated treatment decision.

Pilot Study Finds Differences in Risk Tolerance

While natalizumab was off market, the Mellen Center designed a pilot study to determine MS patients’ tolerance to risk from drug treatment in general and natalizumab in particular.

We designed a questionnaire in the form of a standard gamble paradigm, asking about patients’ risk tolerance. The pilot study included 128 telephone interviews with patients with active MS who had been offered natalizumab when it was first released and had planned to initiate treatment. The design specifically excluded those with benign MS or patients with late-stage disease where active MS therapies were not therapeutically relevant. From that data, we developed a nomogram predicting patient risk tolerance by demographics and disease characteristics.

Having gathered an idea of how patients with active MS tolerate risky therapies, we applied to the National MS Society for funding of a larger-scale study. In this larger study, we accessed the North American Research Committee on Multiple Sclerosis (NARCOMS) MS Patient Registry — a registry of more than 10,000 MS patients treated at MS centers nationwide. Approximately 5,446 patients agreed to participate in the Internet-based study.

The following data was reported at the American Academy of Neurology meeting in April 2011.

Men and the Disabled Tolerate Higher Risk

The first goal involved assessing patients’ overall risk tolerance for any therapy. We probed for risk tolerance of death for a total MS cure. Using a standard gamble paradigm study design, we found that the median tolerance of risk of death for curing MS was 1:10,000. We also found a median tolerance of the risk of PML for the benefits of natalizumab of 1:10,000.

In terms of critical relevance, about one-third of MS patients tolerated the risk of PML associated with natalizumab and would allow treatment with natalizumab therapy given its current risks. We also found that males tolerated higher risk. The median risk tolerance of natalizumab and risk of PML in men was 1:2,000 compared with 1:10,000 in women.

The study also found that a higher amount of disability (as measured through the self-reported Patient-Determined Disease Step score) was associated with greater tolerance of risk. Median risk tolerance for natalizumab went from 1:100,000 in individuals with no difficulties to 1:1,000 for those requiring wheelchair support. Also, we found that those already taking natalizumab were more tolerant of PML risk compared with those not taking the drug (1.750 vs. 1:10,000).
Leading Information Sources and Treatment Decision Influences

We also asked patients where they got their information about MS therapies and who influenced their decision about therapies.

Half of all 5,446 patients noted their neurologist as their primary information source. Another quarter of all patients used the Internet as their leading information source. Further, our study showed that almost three-quarters of patients viewed their neurologist as the main influence on their decision to begin a treatment. Yet one-quarter of respondents did not, and nearly 7 percent saw the Internet as their main influential decision source. Where patients got their information was not always their main influence on decisions. Some sought information elsewhere but went to the neurologist for guidance on their decision.

We did not identify strong predictors of what patient group would use the various information sources. The average age of people who viewed the Internet as their primary source was the same as those who saw the neurologist as the primary source. This was surprising, as we expected younger rather than older patients to prefer the Internet as their primary information source.

There was no gender difference among MS patients regarding where they obtained information or sought influences on decisions. However, patients with longer disease duration were more likely to use their neurologist as their primary source both for information and influence for decisions.

Practice Management Considerations

Our study may enable healthcare providers to better understand the suitability of newer therapies for different patient populations. For example, men do not perceive risk the same way women do. The caveat is that these are just general tendencies. It should not prevent a clinician from offering an appropriate treatment due to an assumption of low risk tolerance. Patients look to neurologists for information and guidance. Though gender does not appear to influence the source of information or decision-making, perhaps this data may highlight an opportunity to provide reliable information sources to women, who tend to be less risk-tolerant overall.

Robert J. Fox, MD, is a staff member at Cleveland Clinic’s Mellen Center for Multiple Sclerosis Treatment and Research and the Department of Neurology. His specialty interests are multiple sclerosis and neuroimmunology. He can be reached at 216.445.6084 or at foxr@ccf.org.

SUGGESTED READING

Minimally Invasive Stimulation of the Sphenopalatine Ganglion for Termination of Cluster and Migraine Headaches

By Stewart Tepper, MD

The sphenopalatine ganglion (SPG), also called the pterygopalatine ganglion in humans, is an extracranial neural structure located laterally in the skull in the sphenopalatine or pterygopalatine fossa (PPF). The SPG is a gateway from the brain stem to outside structures in the skull, such as the lacrimal ducts, the pupils and the eyelids. The SPG contains both sympathetic and parasympathetic autonomic components that not only innervate these peripheral structures but also appear to be part of the final common pathways for both migraine and cluster headaches, two of the most disabling and common primary headache disorders. The prospect of inhibiting this final common pathway to these severe disorders is at the center of several new Cleveland Clinic projects.

A number of procedures are used to inhibit the SPG, and temporarily terminate cluster headaches and migraine. These include SPG blocks, radiofrequency ablation and other forms of destructive surgery. Physicians from Cleveland Clinic are studying ways to safely access the SPG by minimally invasive means and then reversibly inhibit the SPG outflow. The goal is to terminate acute attacks of migraine and cluster headaches by using temporary or continuous stimulation to prevent outflow from the SPG.

This project is very unique to the model of cross-fertilization fostered at Cleveland Clinic, because multiple institutes and centers are involved. A committee met in advance to consider all aspects of the project and included members from Otolaryngology, the Center for Neurological Restoration (neurosurgery and neurology), the Neurological Center for Pain (neurology), Plastic Surgery and Pain Management. Access to the SPG can be through the cheek, an approach championed by Michael Stanton-Hicks, MD, of the Anesthesia Institute, or through the mouth, an approach designed by Frank Papay, MD, of the Dermatology & Plastic Surgery Institute.

The members of the team performed two studies in SPG-inhibitory stimulation delivered reversibly in the operating room, first on chronic migraine, then on cluster headache. Both of these studies were published in Headache, the journal of the American Headache Society. In these studies, patients were taken to the OR, the SPG was instrumented with a temporary stimulator, migraine or cluster headaches were precipitated, and the stimulator was activated. Both studies demonstrated that if the location of the stimulator was correct, acute attacks of migraine and cluster headache appeared to be stopped.1,2

As a result of these two preliminary studies, two more studies are now under way. The first study, for patients with high-frequency episodic migraine, is called an investigational device exemption (IDE) by the U.S. Food and Drug Administration and is being run by a multidisciplinary team from Cleveland Clinic. This study involves placement of the stimulator through the cheek over the SPG, and an implantable programmable generator/battery sited in the chest (Figure 1). For three months, the patients will be able to activate the stimulator and terminate attacks when they occur. For the second three months, the team will turn the stimulator on continuously to see if migraine attacks can be prevented. In addition, the patients will have the option of treating any breakthrough attacks as needed. Following the study, the patients can keep the device.

In the second study, which is under way in Europe, Dr. Papay’s oral approach is being used to place a stimulator over the SPG in cluster patients. The patients have the option of terminating cluster attacks across many months, and then can keep the stimulator at the completion of the study.

A third exploratory cluster headache study using Dr. Papay’s approach is being planned for the U.S. but has not yet been approved by the FDA or Cleveland Clinic.

The team hypothesizes that stimulation of the SPG might interfere with parasympathetic postganglionic outflow, resulting in termination of migraine and cluster. Currently, worldwide there are very few new and preventive treatments being studied in cluster and migraine headaches. Accordingly, devices with minimally invasive implantation techniques may offer new and tremendously exciting alternatives for treating these disorders.
Figure 1: Pictured above is the stimulator, which is surgically inserted through the cheek over the SPG and controlled by a programmable generator that is implanted in the chest.

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REFERENCES


Bringing Focus and Clarity to Deep Brain Stimulation in Parkinson’s Disease

By Jay L. Alberts, PhD

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is one of the more significant advances in treating Parkinson’s disease (PD) to date, but there is evidence that DBS has yet to reach its full potential and produce optimal outcomes. The Department of Biomedical Engineering at Cleveland Clinic Lerner Research Institute and Cleveland Clinic Center for Neurological Restoration intends to explore and refine DBS procedures in order to take full advantage of the technology, improve outcomes and enhance quality of life in patients with PD. The findings from the trial we have designed could have a significant impact on Parkinson’s therapeutic practices.

Cleveland Clinic’s effort will investigate several aspects of DBS therapy. The first investigation will analyze and refine the way the outcomes of DBS are measured. The current practice is to evaluate motor function soon after DBS, followed by a cognitive function evaluation at a later time. We believe this approach has two drawbacks. First, this practice can distort conclusions because the evaluation does not accurately reflect the impact of the therapy on the challenges that PD patients face daily. Motor function and cognitive function are seldom separated in life. A simple action like lifting a spoonful of soup involves both functions; therefore, we are assessing and measuring cognitive and motor function simultaneously. We believe this more comprehensive method of assessment can improve overall outcomes.

A second limitation of current practice is that sequential evaluation often misses or misevaluates the cognitive deficits that can result from DBS, the most common of which are impairments in verbal fluency and working memory. We hope to improve the accuracy of therapeutic analysis by developing a paradigm that allows simultaneous assessment of motor and cognitive performance. Such dual-task testing would reflect more accurately the impact of DBS.

A deep brain stimulation interactive visualization system: Medical imaging data is combined with detailed computer models to customize DBS to individual patients. Anatomical nuclei in the brain (e.g., thalamus — yellow, or subthalamic nucleus — green) are visualized with electrical stimulation predictions (red volume) to help define the optimal electrode location and device settings to maximize clinical outcome.
Deep Brain Stimulation Can Inadvertently Affect Cognitive Function

The cognitive deficits that can follow DBS of the STN appear to originate from the spread or drift of electric impulses from the STN into the adjacent tissues that are associated with cognitive functions. In collaboration with Cameron McIntyre, PhD, from Cleveland Clinic Lerner Research Institute’s Department of Biomedical Engineering, we will analyze with greater precision the nature and extent of deficits associated with both unilateral and bilateral DBS. This analysis will map the total volume of tissue inadvertently affected by electrical impulses. The intent of this analysis is to develop more refined parameters for placing electrodes and also for delivering current at optimal strengths. It is entirely possible, perhaps probable, that minimizing the spread of electrical impulses to nonmotor regions will minimize the therapy’s impact on cognitive function while maintaining its benefits to motor function.

This aspect of the research may also identify a subset of patients in whom unilateral DBS would be sufficient. These patients might be those with asymmetric symptomatology, those who are at a relatively early disease stage and/or older patients who may not wish to exacerbate an existing cognitive deficit.

Data derived from dual testing in differing therapeutic scenarios will allow programs that define therapeutic parameters to be evaluated in terms of real-world outcomes. Findings derived from these analyses should lead to the design of programs that will deliver electrical currents at appropriate strengths and within accurate parameters, thereby minimizing undesirable current spread or drift while maximizing therapeutic benefits.

No New Technology Needed

Currently available software developed by Dr. McIntyre and his team will be used to develop treatment models that will define intended therapeutic parameters with greater accuracy and produce treatment algorithms that are specific to individual patients. These algorithms will necessarily minimize current spread.

We are seeking to create a new tool that can be easily employed in a clinical setting and will allow therapy to be tailored to an individual patient’s symptoms in 30 minutes or less. The programming methodologies developed by this research will be readily available to all institutions utilizing DBS therapy and should be especially beneficial to those lacking extensive experience and expertise in the nuances of DBS programming. Our research in this area is ongoing and supported by a grant from the National Institutes of Health.

Jay L. Alberts, PhD, Edward F. and Barbara A. Bell Family Endowed Chair, is a staff member in Cleveland Clinic Lerner Research Institute’s Department of Biomedical Engineering, and a staff member at Cleveland Clinic’s Center for Neurological Restoration. His specialty interests include the effects of deep brain stimulation on motor function of Parkinson’s disease patients and the effects of unilateral DBS on bilateral motor function. He can be contacted at 216.445.3222 or at albertj@ccf.org.
Targeting Fibrosis in Duchenne Muscular Dystrophy

By Lan Zhou, MD, PhD, and Kerry Levin, MD

In recent years, Duchenne muscular dystrophy (DMD) researchers have been studying the cellular and molecular mechanisms that cause the severe muscle scarring that characterizes the disease. Cleveland Clinic Lerner Research Institute’s Neuroinflammation Research Center is actively involved in this research, which may lead to the development of effective new treatments for this debilitating disease.

Duchenne muscular dystrophy (DMD) is the most common genetic muscle disease, affecting one in 3,500 live male births. It is an X-linked recessive disease caused by a defect in the dystrophin gene. Dystrophin deficiency disrupts the dystrophin glycoprotein complex that normally spans muscle membranes, enabling them to sustain mechanical stretch and contraction.

The disease is characterized by progressive limb, respiratory and cardiac muscle weakness, often leading to premature death when patients are in their 20s. While gene therapy and cell therapy to replace the missing dystrophin gene may someday lead to a cure for DMD, the disease is currently devastating, with no effective therapies. The only relatively effective pharmacotherapy for DMD is corticosteroids, which prolong ambulation but have significant adverse effects.

Understanding Muscle Pathology

Fibrosis, which is defined as hardening and scar formation of tissues in response to chronic tissue injury and inflammation, is a prominent pathological feature of muscle biopsies from patients with DMD. It is characterized by excessive synthesis and deposition of extracellular matrix (ECM) proteins. Fibrosis leads directly to muscle dysfunction and contributes to the lethal DMD phenotype. In recent years, fibrosis has been a major focus of DMD research.

Studies using the mdx mouse model of DMD have demonstrated that ameliorating muscle fibrosis may represent a viable therapeutic approach for DMD. By reducing scar formation, antifibrotic therapies may not only improve muscle function but also enhance muscle regeneration and promote gene and stem cell engraftment. Therefore, understanding cellular and molecular mechanisms underlying muscle fibrogenesis associated with dystrophin deficiency is key to the development of effective antifibrotic therapies for DMD.

Investigating Specific Mechanisms

In a recent study funded by a grant from the National Institutes of Health (NIH), our research team investigated the role of transforming growth factor-beta 1 (TGF-β1) in fibrosis. TGF-β1, a widely expressed multifunctional cytokine, has been demonstrated to be a critical regulator for cell growth and differentiation, inflammation and fibrosis. The level of TGF-β1 expression is upregulated and appears to correlate with fibrosis in DMD muscle biopsies.

Using mdx mice, our research showed that transforming TGF-β1 plays an important role in promoting muscle fibrosis and that inhibiting TGF-β1-signaling pathways represents a promising therapeutic approach for reducing muscle fibrosis in DMD patients.

We were awarded a five-year, $1.7 million NIH grant to study how fibrocytes, an important cellular mediator of tissue fibrogenesis, contribute to DMD muscle scar formation and how this process is affected by certain regulatory proteins known as chemokines. Research has shown that the chemokine system is essential to the recruitment and fibrogenic functions of fibrocytes. Specifically, our team will determine which chemokines and chemokine receptors are involved in the recruitment of these cells from circulation to dystrophic muscles.

We will then investigate whether blocking relevant chemokines or chemokine receptors can reduce the number of collagen-producing cells in dystrophic muscles, ameliorate muscle fibrosis and improve muscle function in mdx mice.

This line of research may lead to the development of novel therapies to treat muscle fibrosis associated with muscular dystrophy and improve muscle function so that DMD patients can live longer and with greater mobility.
Kerry Levin, MD, is Director of Cleveland Clinic’s Neuromuscular Center and Chairman of the Department of Neurology. His specialty interests include electromyography, neuromuscular diseases, myasthenia gravis and peripheral neuropathy. He can be reached at 216.444.8370 or at levink@ccf.org.

SUGGESTED READING


Figures A and B: Collagen III immunostaining showed fibrosis with increased collagen deposition (green) in the endomysium of a dystrophic muscle (A) as compared to a normal control (B).
A collaborative endeavor involving several departments at Cleveland Clinic is pursuing research avenues opened earlier this year with the completion and publication of a study showing that demyelination of hippocampal neurons may contribute significantly to the memory impairment seen in up to 50 percent or more of MS patients. The study’s findings have both diagnostic and therapeutic implications for the 2.5 million people worldwide who are affected by the disease.

Although MS patients in the U.S. are often given an MRI scan early in their diagnosis, a baseline measure of cognitive function is infrequently and/or sporadically established. This may change — and should. The publication of our study can be credited to a call made earlier this year at a special meeting of the New York Academy of Sciences to establish updated tests and metrics for assessing cognitive changes in MS patients.

Unlike the neuronal degeneration seen in Alzheimer’s disease, demyelination associated with MS evidences a relative preservation of hippocampal neurons and axons. The research conducted by Cleveland Clinic’s Department of Neurosciences, the Mellen Center for Multiple Sclerosis Treatment and Research, and the Department of Anatomic Pathology found that even though neurons were preserved, demyelination produced a host of molecular and synaptic changes that could adversely affect neuronal function and cognition.

The study was conducted on postmortem hippocampi from the brains of 22 individuals with MS. Nine hippocampi from individuals without MS served as controls. Demyelination is common in MS and has been identified in 53 to 79 percent of postmortem MS hippocampi. The first observations made in the Cleveland Clinic study were that axonal densities appeared similar in myelinated and demyelinated tissues and that axons looked healthy, with scant evidence of dystrophy or swelling. Dramatic differences between myelinated and demyelinated hippocampi appeared when gene profiles were established. Compared to hippocampi from individuals with no brain disease, expression levels of 799 gene transcripts were different in demyelinated hippocampi, compared to only 32 in myelinated hippocampi. Processes associated with significantly altered genes included intracellular transport (p=0.008), ubiquitin-dependent processes (p=0.001), synaptic transmission (p=0.001), behavioral processes (p=0.032) and learning/memory processes (p=0.028).

The data establish that the loss of myelin leads to alterations in genes involved in specific neuronal functions and that demyelination also alters mRNA that encodes for neuronal proteins involved in synaptic integrity and memory function.

Demyelination decreases levels of proteins essential to anterograde and retrograde fast axonal transport, reduces synaptophysin and synaptogamin, and causes a significant decrease in the number of synapses associated with hippocampal neurons. The consequences of these alterations are a disruption of maintenance functions and the number of hippocampal synapses.

The findings also show that there is a reduction in both fast and slow glutamate neurotransmission, a lower number of glutamate receptors, and a downregulation of glial glutamate transporters and glutamine synthetase. Glutamate neurotransmission has a significant role in synaptic plasticity, memory and cell survival. Hippocampal demyelination was also shown to reduce levels of activated CAMKII and CREB, molecules considered essential to memory and learning.

Two conclusions can be drawn. The first is that the identification of these cellular and molecular changes offers targets for therapies that would restore balance and preserve or perhaps improve memory and other cognitive functions. These findings also call for the development of noninvasive imaging modalities that can distinguish demyelinated hippocampi from myelinated hippocampi at early stages of disease, when therapeutic intervention is likely to be most effective.
Bruce Trapp, PhD, is Chairman of Cleveland Clinic Lerner Research Institute’s Department of Neurosciences. His specialty interests include cellular and molecular biology of myelination, causes of neurological disability in multiple sclerosis and stem cell repair of the central nervous system. He can be reached at 216.444.7177 or at trappb@ccf.org.

REFERENCES


Using Advanced Neuroimaging to Detect Brain Changes in Electroconvulsive Therapy for Depression

By Erik Beall, PhD

Electroconvulsive therapy (ECT) is considered a uniquely powerful modality for treatment of major depressive disorder (MDD), which has an estimated lifetime prevalence of 13 percent in the general population. With a remission rate approximating 80 percent in the acute term, ECT has proved safe and effective for MDD patients who have failed every other intervention, including pharmacotherapy. Yet roughly 20 percent of patients do not respond acutely to ECT and, among those who do, 40 percent do not experience a sustained remission beyond six months. Furthermore, possible side effects — including transient memory loss and behavioral changes — are not negligible.

Inconsistencies in patients’ responses reflect the fact that, despite its undeniable success, this historically controversial therapy works by a mechanism that we do not precisely understand. Thus, progress toward improving treatment is limited more than 25 years after the National Institutes of Health Consensus Development Conference Statement of 1985 asserted that “Much additional research is needed into the basic mechanisms by which ECT exerts its therapeutic effects.”

Data from a preliminary, internally funded neuroimaging study at Cleveland Clinic suggest significant changes in functional brain activation, functional connectivity and gamma amino butyric acid (GABA) levels in response to ECT. These findings appear to differ between responders and nonresponders to therapy. On the strength of these early results, we believe advanced neuroimaging techniques can detect changes in brain activity linked with the therapeutic response to ECT.

We have applied to the National Institute of Mental Health and the National Institute of Biomedical Imaging and Bioengineering with a proposal to use state-of-the-art magnetic resonance imaging (MRI) to better understand the underlying neural mechanisms of successful ECT for major depression and to investigate outcome biomarkers from a single pre-ECT MRI session.

Preliminary Findings

Seven ECT-naïve adult patients (four male and three female) with treatment-resistant depression, for whom a clinical decision to pursue ECT had already been made, were recruited for our study. The subjects were scanned within one week of their first course of ECT and again a few weeks after their final ECT treatment. Informed consent was obtained for the pre- and post-ECT scanning sessions.

Although functional MRI (fMRI) and functional connectivity MRI (fcMRI) have been used to study depression and the treatment effect of antidepressant medications, our study marks the first application of these imaging modalities to investigate ECT. In each scanning session, patients performed three fMRI tasks, developed with the assistance of research neuropsychologist Katherine Koenig, PhD. Two affective picture-viewing tasks required patients to view neutral and unpleasant pictures from the International Affective Picture System and press a button each time a new picture was displayed. A two-back spatial working memory task required subjects to follow a ball as it moved among four boxes. The patients used two button boxes to indicate the ball’s current location during the rest phase and its location two presentations previously during the task phase. Additional imaging was acquired, including spectroscopic measurement in the anterior cingulate cortex and whole-brain high angular resolution diffusion tensor imaging (DTI).

A synopsis of our findings follows:

- **GABA restoration.** A magnetic resonance spectroscopy technique pioneered by Pallab K. Bhattacharyya, PhD, was used to measure neuronal levels of GABA, the brain’s predominant inhibitory neurotransmitter. Numerous studies have linked depression with reduced cortical GABA levels. We observed significant post-ECT normalization of GABA levels in the anterior cingulate cortex, a region implicated in past depression studies and known to be involved in attention and emotional regulation.

- **Activation volume decrease.** Blood oxygenation level-dependent (BOLD) contrast activation levels in response to performance of all fMRI tasks decreased following ECT, dramatically in the case of emotional activation. The change in activation in the orbitofrontal cortex, a region associated with depression and emotional processing, correlated significantly with change in the level of depression.

- **Unchanged white matter tract integrity.** We recorded the first probabilistic tractography-based observations of white matter tract integrity to use high-direction DTI before and after an acute series of ECT. Using transverse diffusivity (water diffusing perpendicular to the primary neuronal direction), we observed no significant change in axonal integrity from pre- to post-ECT scanning, which supports conclusions of prior studies on the safety of ECT.
Left, top (A) and bottom (C): The top image shows the average brain response to performing a spatial working memory task in MDD patients before undergoing ECT. The bottom image shows the average brain response to the same task in the same patients, after ECT.

Right, top (B) and bottom (D): The top image shows the average brain response to viewing unpleasant pictures in MDD patients, pre-ECT. Below is the average brain response to unpleasant pictures in the same patients, post-ECT. In all images, orange corresponds to an increase in blood flow-related activity; blue corresponds to a decrease in activity.
Toward a Deeper Understanding

We plan to build on these early results in a new study that will enroll 60 patients with major depressive disorder and 30 controls. The treatment group will be scanned pre- and post-acute ECT and six months after the course of therapy concludes; the control group will be scanned only once as a baseline comparison. In particular, we seek to:

• **Confirm and increase the specificity of our initial findings on normalization of spectroscopic levels of cortical GABA after successful ECT.**

• **Identify the acute and long-term effects of ECT on abnormal functional and structural brain connectivity.** Our preliminary data suggest that structural connectivity is unchanged by ECT, whereas functional connectivity is dramatically altered. To understand a change in functional connectivity, we need to confirm whether ECT induces axonal damage and whether structural connectivity is a measure of neuronal integrity. We propose to show that ECT produces normalizing changes in functional connectivity driven primarily by cortical, not white matter, changes.

• **Determine whether there are significant predictive differences in MR imaging among nonresponders, acute responders and sustained responders to ECT.** We hypothesize that using advanced imaging modalities (fMRI and resting-state fMRI) in a single pre-ECT session will provide us with a biomarker to predict early in the course of therapy which patients will respond acutely and long-term, as determined by the Hamilton Depression Rating Scale.

An Opportunity for Improvement

A typical course of acute ECT involves a total of six to 12 sessions performed every other day, each combining general anesthesia, motor paralysis with muscle relaxants, assisted ventilation and a brief seizure. A full course of this invasive procedure ranges in cost from $6,000 to $15,000. As noted above, not all patients respond to therapy, and some responders require repeat ECT. An improved understanding of ECT would greatly benefit public health by reducing the expense, the number of unnecessary treatments, the delay in proceeding to potentially more useful therapies for nonresponders, and the risk of morbidity and discomfort.

Erik Beall, PhD, is a project staff member at Cleveland Clinic’s Imaging Institute with a joint appointment at Cleveland Clinic’s Neurological Institute. He is also an assistant professor at Cleveland Clinic’s Lerner College of Medicine. His primary research interests are functional neuroimaging with MRI and development of advanced MRI methods. He can be reached at 216.445.6110 or at bealle@ccf.org.
A Successful Course of ECT

By Mayur Pandya, DO

A 45-year-old woman with a 10-year history of major depression and poor response to pharmacotherapy presented for evaluation. She reported some past benefit from a few medications, but typically the response was inadequate and/or temporary. Trials had consisted of various classes of antidepressants, including selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors, as well as combination and augmentation strategies.

In recent weeks, she had begun to experience a general sense of fear and apprehension, evidenced by nihilistic thinking and a guarded demeanor. She was subsequently admitted and a course of electroconvulsive therapy (ECT) was initiated.

After the first week, her thinking became more grounded in reality, but she continued to display a blunted affect with psychomotor slowing. By the end of the second week, she had a brighter affect with less depression. She was subsequently discharged and completed the ECT course as an outpatient. By the end of the third week, she was socializing with friends and family and denying any continued depressive symptoms.

Her total course consisted of 10 treatments, after which she was placed on a combination of fluoxetine and aripiprazole, with complete restoration of social, occupational and interpersonal functioning.

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Neuromyelitis Optica in Children
By Manikum Moodley, MBChB, FCP, FRCP

Neuromyelitis optica (NMO) is an idiopathic, severe autoimmune demyelinating disorder of the central nervous system characterized by either monophasic or recurrent episodes of optic neuritis and acute myelitis. Unlike multiple sclerosis (MS), NMO commonly spares the brain in its early stages.

NMO has worldwide distribution, representing less than 1 percent of demyelinating illness. NMO disproportionately affects nonwhite populations, in which multiple sclerosis is rare. Once thought to be a variant of MS, NMO is now recognized as a distinct entity with its own clinical, neuroimaging, laboratory and neuropathological findings. NMO affects mainly females and has a median age of onset of 39 years. There are few published reports of NMO in children, and it is frequently misdiagnosed as MS.

Classic and Atypical Syndromes
Classically, NMO has been viewed as an inflammatory demyelinating disorder affecting the spinal cord and optic nerves. In typical cases, the attacks of optic neuritis are more unilateral than bilateral, and the myelitis usually occurs sequentially rather than simultaneously. The intervals separating these events can be months, years or decades. Recently, it has been shown that other areas of the central nervous system may also be affected by the inflammatory process. Painful vision loss with severe symmetric paraplegia/paraparesis, sensory loss and sphincter disturbance are typical features of NMO.

Atypical forms of the disease include single or recurrent attacks of longitudinally extensive transverse myelitis or optic neuritis that can be either unilateral or bilateral. Other atypical syndromes include brain stem and area postrema involvement resulting in nausea, vomiting, hiccups or severe neurogenic respiratory failure; narcolepsy-like syndrome; encephalopathy with coma-like episodes due to extensive hemispheric lesions; posterior reversible encephalopathy-like lesions; and vasogenic edema. NMO can also coexist with other autoimmune disorders, in particular, systemic lupus erythematosus, Sjögren’s syndrome, celiac disease, thyroiditis and myasthenia gravis.

Neuroimaging Investigations
Brain MRIs at onset are typically normal, except for optic nerve enhancement. An exception is brain stem lesions, occurring in isolation or as an extension of the longitudinally extensive cervical lesion. Brain lesions occur in 60 percent of NMO patients and are distinct from MS lesions (Figures 1, 2a and 2b).

MRIs of the spine show lesions that are also distinct from those of MS. The lesions are centrally placed and longitudinally extensive, span three or more contiguous vertebral segments, and are associated with cord edema and contrast enhancement on T2 weighted images (Figure 3). In MS, the myelitis is asymmetric and the lesions rarely exceed one or two vertebral segments in length.

Laboratory Studies
CSF pleocytosis greater than 50 cells/mm³ with a high proportion of neutrophils is a characteristic feature of NMO, in contrast to MS, where a pleocytosis of this degree and neutrophil predominance is unusual. CSF oligoclonal bands (OCBs) are detected in only about 15 to 30 percent of patients with NMO. In contrast, oligoclonal bands are detected in up to 90 percent of patients with MS. In addition, OCBs in NMO usually disappear with time, unlike the OCBs in MS. The discovery in 2004 of a serum autoantibody biomarker (NMO IgG) further enhanced the understanding and categorization of NMO. This autoantibody is 73 percent sensitive and 91 percent specific for clinically diagnosed NMO. It is important to note that the NMO IgG antibody has not been detected in any autoimmune disorders that lack manifestations of NMO.
Immunopathogenesis

The NMO antibody is directed against the water channel aquaporin-4, which is concentrated in the astrocytic foot processes at the blood-brain barrier. Aquaporins are membrane water channel proteins important in maintaining brain water homeostasis.5, 6

The characteristic lesions of NMO occur at sites of high aquaporin-4 expression such as the optic nerves, spinal cord, brain stem, periventricular areas and hypothalamus (Figure 4).

Diagnosis

Following the discovery of the NMO IgG antibody, Wingerchuk and colleagues have proposed revised diagnostic criteria for definite NMO. Their criteria require 1) optic neuritis and myelitis and 2) at least two of the following three supporting criteria: MRI evidence of a contiguous spinal cord lesion three or more vertebral segments in length; a brain MRI nondiagnostic for MS at the onset of the disease, and detection of NMO IgG in the serum.

The MRI brain lesions characteristic of NMO occur adjacent to the ventricular system at any level but more commonly around the third and fourth ventricles and aqueduct of Sylvius than around the lateral ventricles. The corpus callosum is rarely involved. These MRI brain lesions characteristically mirror the periventricular and hypothalamic location of aquaporin-4.

Therapeutic Options

Early and accurate diagnosis of NMO is imperative because it lacks the progressive course of relapsing/remitting MS and thus warrants aggressive therapy. Acute attacks are treated with corticosteroids, such as intravenous methylprednisolone. Plasmapheresis is indicated in patients who have severe, worsening or corticosteroid-refractory acute attacks.

For relapse prevention in the pediatric population, immunosuppression with azathioprine (CellCept®) is an appropriate alternative immunosuppressive agent, but determining optimal therapeutic protocols for NMO in children will require randomized controlled trials. For resistant cases, rituximab may be a useful agent, though concern about the emergence of progressive multifocal leukoencephalopathy and lack of long-term safety data negates its frequent use, especially in children.

Conclusion

NMO is an uncommon but severe CNS demyelinating disorder with an invariably poor prognosis. Recent reports have highlighted its presentation in pediatric patients. Its clinical manifestations are diverse, and in about 25 percent of cases it is associated with other autoimmune disorders. The NMO IgG antibody is a valuable tool to define an extended spectrum of NMO-related disorders with the hope of initiating timely and targeted therapy. Data on treatment of NMO, especially in children, are sparse, and randomized controlled trials on this disease in children have not yet been performed.

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Residual dysfunction in the paretic hand following a stroke is an important predictor of poor quality of life and affects a staggering proportion of stroke survivors. Research conducted by a collaborative team from Cleveland Clinic’s Department of Physical Medicine and Rehabilitation and Imaging Institute addresses an important problem related to residual disability — revealing and modifying its underlying mechanisms to facilitate recovery.

Research has identified a mechanism perpetuating residual dysfunction: maladaptive transcallosal inhibition (TCI). The contralesional (intact) motor cortex exerts abnormal inhibition via transcallosal pathways (through the corpus callosum connecting the stroke-affected and unaffected hemispheres) upon the ipsilesional (stroke-affected) motor cortex. Although contemporary rehabilitation and advanced techniques, such as neuromodulation involving brain stimulation, attempt to reduce maladaptive TCI, effects are modest, variable and poorly replicated in large-scale trials. We are addressing this research problem by using two exclusive yet complementary aims — accurate examination of transcallosal connectivity (TCC) and modulating TCI to facilitate stroke rehabilitation.

**Implications for Scientific Knowledge and Clinical Practice**

Inconsistency and ineffectiveness of contemporary rehabilitation and brain stimulation raise doubts about their ability to target TCI. If successfully validated, our novel imaging markers of TCC will either help confirm such speculations or encourage the study of alternate mechanisms or treatment strategies. If successful, our imaging markers will be optimized for cost-effectiveness in the future and serve as routine assessment tools in clinical practice for defining rehabilitation prognosis and helping develop new methods for modulating TCI directly through noninvasive and invasive brain stimulation.

**Modulating TCI to Facilitate Recovery in Stroke Rehabilitation**

Contemporary rehabilitative methods of normalizing TCI in stroke address residual deficits by promoting use of the paretic upper limb during restraint of the nonparetic limb. Despite promising evidence, clinical utility of these methods is limited due to labor-intensive protocols that are expensive and impractical to follow. Furthermore, variable outcomes and persistent deficits prevent drawing definitive conclusions about efficacy.

Delivering cortical stimulation may accelerate or enhance normalization of TCI in rehabilitation, making it less labor-intensive and more effective in promoting function. In fact, animal and preclinical studies show that stimulating surviving motor cortical regions and perilesional areas during rehabilitation offers a synergistic functional advantage compared to rehabilitation delivered alone.

Despite its preliminary success, the efficacy of combining cortical stimulation and rehabilitation remains unconfirmed in large-scale studies. In our research, we are addressing numerous inconsistencies in past research that may explain these null findings. Our efforts include 1) choosing alternate loci of stimulation based on their potential to survive and function vicariously for lesioned areas, 2) adopting methods of cortical stimulation that can be applied concurrently in rehabilitation, and 3) examining comprehensive functional and structural neural indices that define response to the synergism of stimulation and rehabilitation.
By aiming to improve the efficiency and effectiveness of current methods of rehabilitation, our paradigm intends to promote the therapeutic utility of current interventions, thereby reducing excessive healthcare costs associated with stroke. Furthermore, the scientific knowledge created in our research will foster an understanding of comprehensive mechanisms of recovery, ultimately developing paradigms optimized to patients’ lesions, function and neural resources.

Future Directions

Stroke offers an excellent clinical-theoretical model to explore the functions of different regions of the brain during movement, their interactions in neuromotor recovery and the effects of differentially weighting those networks to further facilitate function. Our research in stroke has helped us prepare for translating learned concepts to other spheres of neurological rehabilitation, such as impaired upper limb control in incomplete spinal cord injury and geriatric rehabilitation. Through funding from the National Institutes of Health, the Department of Defense, and the Clinical and Translational Science Initiative at Cleveland Clinic and collaborative support from a multidisciplinary team of Cleveland Clinic investigators — including Frederick Frost, MD; Andre Machado, MD, PhD; Mark Lowe, PhD; and Stephen Jones, MD, PhD — we believe we have key opportunities for diversification of our research portfolio.

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Figure 1: Functional connectivity (FC) MRI generated with left primary motor cortex as seed for analysis (green arrows), during rest (top) and continuous finger tapping (bottom). Resting fc-fMRI shows coupling between numerous brain regions including visual (red arrows) and motor (green arrows). Our paradigm of mod-fc-fMRI instead focuses FC specifically to bilateral motor areas, as a surrogate marker for transcallosal connectivity (TCC).

Figure 2: Probabilistic tractography map of transcallosal white matter pathways between bilateral motor cortices, used to measure TCC.
Establishing Regional Stroke Care Centers

By Stephen Samples, MD; Peter Rasmussen, MD; Nancy Papesh, BSN, CFRN, EMT-B; and Brian Monter, MSN, RN, MBA

In early 2009, Cleveland Clinic Neurological Institute made a significant commitment to building and developing a stroke system of care throughout the Cleveland Clinic health system. Led by Cleveland Clinic’s Center for Regional Neurosciences and Cerebrovascular Center, the primary goals were to gain The Joint Commission Primary Stroke Center certification at all Cleveland Clinic community hospitals in Northeast Ohio, develop three regional hubs for acute and elective interventional care, and create standardized carepaths and documentation to enhance quality and consistency of care across the health system.

Stroke affects an estimated 795,000 individuals annually. It is the fourth leading cause of death and the leading cause of adult long-term disability in the United States. According to the American Heart Association, the economic cost of this devastating disease was an estimated $73.7 billion in 2010. These alarming statistics reflect the human and economic cost of stroke, and with an aging population, stroke’s impact is expected to increase progressively over the next 50 years. With healthcare reform on the horizon, this disease deserves significant attention from both the healthcare sector and policymakers.

Primary and Comprehensive Stroke Centers

As advancements in acute stroke care have emerged, so has the need for specialized centers of excellence to provide efficient and coordinated care. To receive Primary Stroke Center certification from The Joint Commission, hospitals are expected to implement national clinical practice guidelines and collect, monitor and report on at least eight core clinical performance measures on a quarterly basis. Among the most important facets of the program are:

- Continuous iterative evaluation of data to improve compliance
- Ability to administer intravenous thrombolytics in a timely manner
- Dedicated team and care area for stroke patients

Comprehensive centers are capable of delivering the full spectrum of stroke care, including emergent neuro-interventional treatment of ischemic stroke for patients with severe cerebrovascular disease. The Joint Commission is planning to release an advanced certification for comprehensive stroke center designation in the near future. Behind this additional certification is the expectation that stroke patients will receive the best possible care at the right place, at the right time, leading to the best chances for positive outcomes.

Time Is Brain

Acute stroke is a neurological emergency and requires urgent treatment, unlike many other illnesses where an elective referral pattern of care delivery prevails. It is undesirable to have a patient travel over any unnecessary time or distance to be treated at a large quaternary referral center hospital if the same emergent care can be provided at a closer alternate location.

To address the issue of urgency, Cleveland Clinic developed a three-tiered system for stroke care across its network of community hospitals, all of which are Primary Stroke Center-certified or in the process of becoming so, leaving the centrally located main campus as a quaternary site for the most complex cases. By providing comprehensive, emergent treatment of acute ischemic stroke at three hospital locations, Cleveland Clinic ensures that every patient in the county has access to high-level acute stroke therapy within 10 miles or 20 minutes of home. Because time is brain, precious minutes saved translate into potentially improved outcomes and stroke survival rates.

Next, stroke teams were established at nearly every Cleveland Clinic community hospital and staffed almost exclusively with Cleveland Clinic neurologists. In keeping with the “time is brain” concept, select community hospitals with significant patient volumes and regional hubs followed a neurology hospitalist model similar to that found in large academic settings, with an on-site neurology presence dedicated solely to inpatient work and response to acute stroke. This commitment translated into tangible improvements in thrombolytic and neuro-interventional therapy use throughout Cleveland Clinic’s health system.

Enterprise Achievements

To help meet the challenge of regionalization of care for a complex emergent neurological illness, quarterly enterprise forums were established where the community hospitals develop and integrate best stroke care practices. The forums provide an interactive setting for exchanging information between the teams. Teams then adapt information to suit the unique care formats and availability of imaging personnel at each facility.

Standardized order sets have been developed with the input of the Vascular Neurology staff, Regional Neurology staff and various private practice neurologists in the community. A regionwide acute stroke imaging triage algorithm was also established and approved, and a standardized regional hospital system stroke carepath is being developed. Stroke performance metrics are reviewed and changes in practice are approved and implemented by stroke leaders throughout the health system. All participating hospitals are members of the Ohio Coverdell Acute Stroke Registry Council.
Evidence of the success of this approach may be seen in a 36 percent increase in IV thrombolysis and a 20 percent increase in IA thrombolysis across the health system. Additionally, increased core measure compliance can be seen in the creation, approval and adoption of a systemwide nursing dysphagia screen, which is expected to improve the rate of aspiration pneumonia in our patients. Currently, six of nine hospitals in the health system are certified as Primary Stroke Centers, with the rest scheduled to achieve certification in 2012. Regional integration has driven appropriate staffing, coverage and alignment of neuroscience services and is a testament to the collaboration between Cleveland Clinic’s Cerebrovascular and Regional Neurosciences centers.

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The Medina Experience

Perhaps the most exciting advancements in regional stroke care development have been at Medina Hospital, located 35 miles from Cleveland Clinic’s main campus, which had never given IV r-tPA more than twice in any given year prior to joining Cleveland Clinic in 2009. Upon establishing an acute stroke program in 2010, Medina Hospital delivered IV r-tPA to patients who presented within the treatment window for acute stroke five times in the last four months of 2010. The three major contributing factors to this success were implementation of standardized protocols, order sets and carepaths. Cleveland Clinic’s Center for Regional Neurosciences neurologists exclusively provided 24/7/365 on-call neurology consultation and acute stroke call to the emergency department, and the hospital also agreed to participate as a pilot site for the Cerebrovascular Center’s Telestroke Program for telemedicine coverage. In the first seven months of 2011, this team had administered IV r-tPA to 11 patients, an astounding number of cases for this 120-bed hospital. Medina Hospital has applied for Primary Stroke Center certification through The Joint Commission and expects a site visit in the first quarter of 2012.
Impact of Concomitant Cardiopulmonary Abnormalities in Obstructive Sleep Apnea

By Nancy Foldvary-Schaefer, DO, MS

Sleep apnea (SA) is a common disorder affecting approximately 24 percent of men and 9 percent of women. The American Academy of Sleep Medicine estimates that nearly 90 percent of affected individuals are undiagnosed and, therefore, untreated.

The prevalence of SA is likely to be higher in certain medical and surgical populations as a result of comorbidities including obesity, heart failure, coronary artery disease and chronic obstructive pulmonary disease. Despite this, SA assessment is not performed routinely in high-risk populations, including surgical populations that may be at risk for complications after general anesthesia. In a recent cardiac surgery series reported by Cleveland Clinic investigators, patients with SA had higher rates of mediastinitis and encephalopathy and longer postoperative ICU stays than did those without SA.

Awareness of the dangers of undiagnosed SA is increasing. In 2006, the American Society of Anesthesiologists (ASA) issued a practice guideline highlighting the need for more aggressive preoperative, intraoperative and postoperative intervention for surgery patients with SA. Diagnostic polysomnography (PSG) is traditionally conducted in the outpatient sleep laboratory, but preoperative assessment may be preferred in certain hospital situations.

Investigators from Cleveland Clinic, Johns Hopkins Sleep Disorders Centers and CleveMed Inc., a developer of wireless polysomnographic technology, joined forces to study the value of in-hospital SA assessment in cardiac surgery patients. The study utilized the Crystal 20-H™ device and implemented several upgrades to allow for wireless data transmission dedicated to the hospital environment. One hundred seven patients admitted for coronary artery bypass graft or valve replacement surgery underwent preoperative PSG. Studies were performed in the hospital room and remotely monitored in real time from the sleep laboratory using a wireless, 14-channel PSG acquisition system.

Several outcomes were tracked postoperatively during a 30-day follow-up, including length of ICU stay. More than 71 percent of the patients were found to have SA, and over 30 percent had severe SA (defined as 30 or more respiratory events per hour of sleep). Cardiac surgery patients with severe SA stayed in the ICU almost one day longer at both hospitals than did those without SA. While the results are preliminary, this study shows that SA is common in patients undergoing cardiac surgery procedures and may lead to extended ICU stays. The study also confirms the feasibility and quality of preoperative PSG recorded in the hospital and monitored remotely.

Nancy Foldvary-Schaefer, DO, MS, is Director of Cleveland Clinic’s Sleep Disorders Center. Her specialty interests include sleep disorders, epilepsy, and the relationship between sleep and epilepsy. She can be reached at 216.445.2990 or at foldvan@ccf.org.

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Pulmonary Hypertension as an Indicator of Reduced Survival in OSA Patients

By Omar Minai, MD

The close association between SA and cardiovascular and parenchymal pulmonary diseases (such as COPD and IPF) is well-recognized. The true prevalence of the overlap and its clinical impact remains less well-defined. Investigators at Cleveland Clinic Sleep Disorders Center have been interested in determining the prevalence and clinical impact of the overlap between sleep apnea and cardiovascular and pulmonary comorbidities. In a study of patients with obstructive sleep apnea (OSA) undergoing right heart catheterization, Minai et al. were the first to show that the presence of pulmonary hypertension (PH) is an indicator of reduced survival (Figure 1). This was true of patients with pulmonary arterial hypertension and those with pulmonary venous hypertension. The investigators also found that the presence of PH was not directly related to the severity of OSA and that OSA patients with PH had more nocturnal hypoxia compared to patients without PH. In a follow-up study presented at the annual Professional Sleep Societies 2011, they found that degree of oxygen desaturation and abnormal pulmonary hemodynamics (such as stroke volume and pulmonary vascular capacitance) were important predictors of survival in patients with OSA.

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Figure 1: Kaplan-Meier survival estimates in 83 patients with OSA (A) with and without PH and (B) without PH compared with those with PAH and PVH.
Robots Bring New Level of Sophistication to Biomechanical Testing

By Robert McLain, MD

When Czech playwright Karel Čapek introduced the term “robot” in his 1921 play Rossum’s Universal Robots, he was talking about the production of human-like machines in a factory environment. Today, nearly a century later, factories full of industrial robots produce some of the most complex machines and products mankind has ever used. Robots are everywhere! Yet the use of robots as sophisticated “assistants” in biomechanical testing has come along only recently.

The human spine is a complex structure composed of active and passive elements stacked in an asymmetric column. In the diseased state, disturbance of these elements can lead to a variety of spinal abnormalities or pathologies. To understand these disorders, it is often helpful to compare the biomechanical behavior of motion segments of a normal, intact spine to those of diseased spines affected by degeneration, surgical decompression or spinal instrumentation. To objectively assess the effects of injury or surgery on the stability of the spine, biomechanical studies of cadaver or animal spines, or vertebral analogs, can be carried out under carefully controlled circumstances. How researchers obtain the load-displacement data at the heart of these analyses is controversial: Does one measure displacement at maximum load or measure load at maximum displacement?

A Dual Approach to Biomechanical Analysis

One of the ways that robotic testing may change biomechanical analysis for the better is by allowing researchers to use both strategies at the same time. This allows investigators to control the movement of the specimen and the displacement of segments in a more natural way.

This option is new: Until very recently, biomechanical testing was possible in only one of two modes — load-controlled analysis (how much displacement would occur with a given load) or displacement-controlled analysis (how much load is required to achieve a given displacement).

In testing the relationship between applied loads and the displacement they cause in spinal segments, the results observed provide a quantitative measure of the stiffness or flexibility of the spine in that condition. Increased stiffness compared to normal generally indicates an abnormal condition such as arthritis or fusion. Increased flexibility may indicate ligamentous disruption or destruction of bone. Increased stiffness following spinal instrumentation generally reflects superior fixation strength. The assessment of biomechanical integrity of the spine in each of these situations is based on the quantitative measurement of the load-displacement response.

Some authors have argued for load-controlled testing on the merits that the method is relatively convenient at small load magnitudes and that it produces natural-looking motions. Unfortunately, our limited understanding of in vivo conditions has made it difficult to apply complex and accurate loads to the spinal segments. If the natural loads are not accurately simulated, it is possible that misleading results could be obtained using this method. Further, if the target load for the test exceeds the strength of any one of the testing constructs, the specimen is likely to fail, invalidating the experiment.

The alternative has traditionally been displacement-controlled methods. Displacement-controlled testing offers advantages in conditions with near-zero stiffness. In testing a fractured specimen, for instance, even a small peak load might result in excessive displacement or disruption of the specimen if there are no other limits in place. A testing system controlled by a specific peak load might never approach that stopping point in a very flexible construct or specimen, at least not until the specimen had been deformed far beyond normal limits. In the other extreme, the very light loads required to test fragile or unstable specimens are often not enough to show a significant difference between different spinal fixation methods. The displacement-controlled methodology, which carefully defines the extremes of movement through which the testing apparatus will force the specimen, provides a means for successfully testing in these extreme conditions. Until recently, researchers have had to choose the best-fitting or the least-flawed methodology for whatever experiment they were doing.
Hybrid Control Offers Sophisticated Simulation of Spine Movement

Robotic testing methods may have solved this dilemma. Sophisticated programming and feedback systems now allow us to apply load-controlled methodologies in circumstances where spinal rigidity may be high, yet we can still provide displacement-controlled limits that prevent damage and disruption of adjacent, more fragile segments. This “hybrid” control allows robotic testing to more closely simulate the complex coupled motions of the actual human spine in real life.

On top of this, the robot’s ability to simultaneously apply rotational, axial and shear loads allows a more sophisticated level of testing than possible before.

Though Karel Čapek’s play ends with a robotic rebellion and the extinction of the human race, things look a bit rosier for people when it comes to robo-mechanical testing. Early results in studies at the Cleveland Clinic Spine Research Laboratory have shown that robotic systems are versatile, sensitive and adaptable to a wide variety of spinal segments and testing arrays. Studies are currently under way on lumbar fixation, cervical mechanics and motion-preserving implants. Robo-mechanics looks to be a boon to both researchers and patients alike.

Robert McLain, MD, is a staff member at Cleveland Clinic Center for Spine Health. His specialty interests include back and neck surgery, reconstruction and disc surgery, minimally invasive disc and fusion surgery, treatment of spinal tumors and deformity, cervical and lumbar artificial disc replacement, X-STOP, and kyphoplasty. He can be reached at 216.363.2410 or at mclainr@ccf.org.
Cleveland Clinic Concussion Center at the Epicenter of Concussion Crisis

By Jay L. Alberts, PhD; Adam Bartsch, PhD; Edward Benzel, MD; and Richard Figler, MD

Cleveland Clinic Concussion Center was formed in 2011. The Concussion Center was created amidst an increasing focus on the brain health implications of concussion in military personnel, the general population and, particularly, in youth, collegiate and professional athletes. Recently, as a possible sequela of the cumulative effect of clinically symptomatic concussive and clinically silent sub-concussive impacts, the careers (and in some cases the lives) of a number of high-profile football players have ended prematurely.

Concerns regarding the immediate and long-term effects of multiple concussive and sub-concussive impacts on the brain health of football players have led to an escalating demand for improvements in helmet design and testing standards as well as a re-evaluation of athlete training regimens and on-field, safety-related rules and regulations. In spite of the heightened awareness surrounding concussion, much remains unknown about the risks of football-related head impact dosage. In 2011, multiple state legislatures, including Ohio’s, and the U.S. Congress recognized the urgent need to help protect millions of children participating in organized tackle football programs. They have introduced legislation that mandates the development and employment of standards for the evaluation of, and the protection provided by, youth football helmets. In addition, criteria for identifying and managing youth athletes who have incurred concussion have been developed and introduced.

Participants in Cleveland Clinic Concussion Center include Cleveland Clinic’s Center for Sports Health, Center for Spine Health, Center for Neurological Restoration, Department of Neurosurgery, Department of Orthopaedic Surgery, Department of Biomedical Engineering and Spine Research Laboratory (SRL) at Lutheran Hospital. In addition to providing superb clinical diagnosis and care, the members of the Concussion Center team are seeking answers to clinical problems that have evaded solution, and an understanding of the traumatic neuro-mechanics of concussion and sub-concussive injury. These stakeholders have come together to function as a unit within Cleveland Clinic Concussion Center and are uniquely poised to take advantage of several critical competencies. These include clinical care, clinical research, basic science research, innovation, and community outreach and advocacy.

Clinical Care

Clinical care is the center of focus for Cleveland Clinic Concussion Center. The goal of clinical care is the safe return of a concussed athlete to competition, along with a reduction in the potential for further injury and a decrease in the potential effects that can be felt on the field and in the classroom. This is accomplished through the education and awareness of coaches, players, parents and clinicians. Early identification and intervention with appropriate management steps typically lead to an earlier, safer return to activity. The multidisciplinary team that has formed and the clinical care pathway that is in development help expedite care at all levels, whether it is the initial evaluation and management or the potential referrals that a more complex concussion may warrant.

Figure 1: Impacts conducted with leather and modern helmets (above, left) showed that the leather helmet impact dosage was on par with modern “varsity” helmets (above, right).
Clinical Research

A 2011 NFL Charities grant is currently funding ongoing research by Cleveland Clinic Concussion Center researchers regarding concussion risk in youth sports. This work is specifically focused on the determination of factors that affect youth safety and helmet protection.

Basic Science Research

Cleveland Clinic Concussion Center is actively involved with several domains of basic science concussion research. Football helmet testing at SRL has shown that in certain instances, pre-World War II-era leather helmets performed on par or better than some helmets currently used in high school, college and professional football regarding the attenuation of energy imparted to the brain as observed through mechanical testing (Figures 1 and 1a). Similar SRL studies on boxing and mixed martial arts protective padding demonstrated that padding the head and hand did not always appreciably reduce risk of head and neck trauma (Figure 2).

Further-reaching research activities are ongoing at Cleveland Clinic. For instance, Michael Phillips, MD, Vice Chair of Research and Academics in the Department of Diagnostic Radiology, is currently actively investigating advanced brain injury neuroimaging. Damir Janigro, PhD, Staff in both the Cerebrovascular Center and Lerner Research Institute’s Department of Cell Biology, and Nicola Marchi, PhD, Project Staff in the Department of Cell Biology, are exploring brain injury blood biomarkers. Each of these projects plays a seminal role in unlocking the mysteries of concussion and its prevention, diagnosis and management.

Figure 1a

Figure 2: Studies with boxing and mixed martial arts showed that padding did not always significantly protect the brain or neck.
Innovation

Researchers at Cleveland Clinic Concussion Center have focused on the development of unique technologies that are designed to improve the quantitative assessment of concussion injury risk exposure and concussion-related injury diagnostic accuracy. The Intelligent Mouthguard, an impact dosimeter, was conceived and designed at Cleveland Clinic (Figure 3). Aided by Cleveland Clinic product development funds and the NFL Charities grant, the first in vivo Intelligent Mouthguard impact dosage data was collected at the end of 2011. Finite-element analysis strategies modified at Cleveland Clinic have enhanced the ability to pinpoint “hot spots” within the brain, which in turn facilitates more accurate and clinically meaningful injury analysis (Figure 4).

Methods of Assessment

Jay Alberts, PhD, Associate Staff in the Department of Biomedical Engineering and Center for Neurological Restoration, and his team have developed a concussion assessment and management system on the iPad® 2. The Cleveland Clinic Concussion (C3) app is designed to test the major symptoms of concussion, including postural, stability and cognitive and motor functioning. The C3 app is currently being tested in high school and college athletes within the Cleveland metropolitan area. This tool will provide clinicians with an objective and quantitative assessment of the major symptoms of concussion that can be used in return-to-play decision-making.

Community Outreach and Advocacy

Cleveland Clinic Concussion Center clinicians have been heavily involved with community outreach through radio talk shows, seminars and youth safety legislation advocacy at the state and national levels. These substantial efforts are truly representative of the center’s commitment to safety and brain health.

Cleveland Clinic Concussion Center is uniquely poised to help resolve the concussion crisis. There are very few places where such a unique and talented selection of clinical and basic science researchers can rub elbows on a daily basis. With continued cross-pollination of myriad concussion domains within the center, much will be done to ensure that athletic competition is as safe as possible and that long-term brain health is preserved in all who participate in contact sports.
Jay L. Alberts, PhD, Edward F. and Barbara A. Bell Family Endowed Chair, is a staff member at the Department of Biomedical Engineering at Cleveland Clinic Lerner Research Institute and a staff member at the Center for Neurological Restoration. He can be contacted at 216.445.3222 or at albertj@ccf.org.

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REFERENCES


Figure 4: Finite-element analysis allows for theoretical injury hot spot identification from actual on-field or laboratory impact dosage data.
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3rd Annual Neurology Update  
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