Rethinking Treatment of Cognitive Disorders

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On the cover: A segmented image of the brain, used to measure brain volume and hippocampal volume changes in Alzheimer's disease.
Dear Colleagues

As we move toward the second decade of the 21st century, we face a potentially devastating healthcare crisis that is unique to the era of modern medicine and longer lifespans. Each day, more than 7,900 Americans attain age 60, according to estimates. As that number grows, so, too, does the prospect of a healthcare system overwhelmed by a relentless increase in the prevalence of neurocognitive disorders, primarily Alzheimer’s disease.

Those of us 50 and older worry about this individually, fearing that misplaced keys or a forgotten name is the first sign of the inexorable downward spiral. Yet, we have not faced up to it as a society and, as a result, we rush toward this day of reckoning without a well-organized approach to mitigate the inevitable drain on public and private resources, as well as the personal pain for patients and their families.

A ray of light amid this gloom comes with the expanding body of research showing that we can delay onset of a range of cognitive diseases, thus adding years of functional life for people in the initial stages. Early diagnosis and prognostication also can guide us in choosing where and how to direct our resources for maximum effectiveness.

Evidence continues to accrue that the multidisciplinary approach we bring to treating many physiological diseases is likewise appropriate for delaying and ameliorating the symptomology of cognitive loss syndromes. Ideally, this approach would comprise:

- neurology for patient evaluation
- neuropsychology for quantitative measurements of cognition
- neuroimaging to assess progressive morphologic or functional alterations, possibly enabling predictions earlier than with clinical assessment alone
- internal medicine and geriatrics to manage comorbid conditions such as diabetes, obesity and hypertension
- physical medicine and rehabilitation to improve and maintain healthy lifestyles
- cognitive rehabilitation, which we know has some effect, particularly on Mild Cognitive Impairment
- nursing, social work and allied health professions
- beyond the clinical side, basic and translational research

At Cleveland Clinic, our institute model groups multiple specialties together in a collaborative structure to share and advance knowledge for the benefit of our patients. With this template, we have established the Lou Ruvo Center for Brain Health in Cleveland and Las Vegas. Our goal in Cleveland Clinic’s Neurological Institute is to develop the leading diagnostic and prognostic facility for early identification and treatment of patients with cognitive disorders and care of their family members, as well as continued research and education.

We cannot yet prevent or cure these insidious diseases that assault the brain and systematically destroy the essence of what makes us human: the ability to think rationally. In this issue of Pathways, however, we highlight new developments that give cause for hope as we brace for the challenge of caring for an aging population.

Also in this issue, we report on minimally invasive technology for treating recurrent or progressive glioblastoma tumors; promising research on a marker for predicting cerebral vasospasm after subarachnoid hemorrhage; stereoelectroencephalography for treatment of refractory epilepsy; a novel investigation of the pathophysiology of dystonia; progress toward oral therapies for multiple sclerosis; and more.

I hope you enjoy these articles, and I welcome your comments.

Sincerely,

Michael T. Modic, MD, FACR
Chairman, Cleveland Clinic Neurological Institute
A Multimodal Approach to Treatment of Alzheimer’s Disease

By Randolph B. Schiffer, MD

Alzheimer’s disease (AD) has proved to be a strange, difficult syndrome to approach scientifically and to treat medically. Despite the expenditure of hundreds of millions of research dollars in the past 20 years, only the cholinesterase inhibitors and memantine have advanced as useful treatments, and their clinical effects are minimal.¹ Yet, unlike most other major neuropsychiatric syndromes, AD seems susceptible to modulation by, and perhaps treatment with, nonpharmacologic intervention domains. This hypothesis has guided the establishment of Cleveland Clinic’s Lou Ruvo Center for Brain Health.

Several therapeutic modalities — cognitive activity, physical activity, management of cardiovascular risk factors, cognitive-enhancing medications — have garnered some support in the medical literature on AD, though none has shown strong, persuasive evidence of efficacy in treatment of the disease or of pre-Alzheimer’s syndromes.

While developing a cognitive therapies program at Texas Tech University Health Sciences Center, however, we wondered if a combination of all four modalities might produce additive, or even synergistic, benefits for selected patients with cognitive loss syndromes. Thus, we developed the initial outline of a “multimodal therapy algorithm” for treatment of cognitive deficit disorders, notably for mild AD and its progenitor syndromes. Now, we intend to build on this groundwork.

Cognitive Activity Therapy

The Memorcize™ Training Program uses a domain-specific, manualized set of cognitive exercises adapted to each individual’s cognitive loss profile in a series of eight one-hour sessions. The cognitive profile is generated from the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), which is administered to each subject on the first visit. The RBANS provides information on functioning in five cognitive domains: immediate memory, visuospatial/constructional, language, attention and delayed memory. We have reported good sensitivity and specificity of this instrument to the cognitive impairments of early AD.² After the patient’s initial visit, six therapy sessions are conducted at weekly intervals. The regimen for each session includes two cognitive exercises selected from the Memorcize manual. These exercises are allocated to the two weakest cognitive domains for each patient. We have unpublished data concerning the six-month effectiveness of the Memorcize program for a cohort of the first 18 early AD patients who underwent cognitive exercise (Figure 1).

Physical Activity Therapy

The physical activity algorithm has two phases. The first phase, training, involves three 30-minute sessions per week for 12 weeks. Our aim is to evaluate and enhance cardiovascular fitness.

After medical clearance from the patient’s primary care physician, we perform a baseline cardiovascular fitness evaluation and compute a targeted heart rate range. Each subsequent exercise training session is rated, with a treatment goal of a 3 (moderate) or 4 (somewhat hard) rating on a “Perceived Exertion Scale.”
The second phase, continuation, is individualized, but the goal for all patients is to continue the exercise regimen established during the training phase in public facilities close to home. We monitor success by re-evaluating patients' cardiovascular fitness at six-month intervals.

We do not have discrete evidence of the effect of this intervention in our treatment population.

Management of Vascular Risk Factors

We do not have evidence-based knowledge concerning how best to intervene with regard to vascular risk factors in the prevention or treatment of the dementias. Our present approach is to key our interventions on measured vascular parameters, in accordance with the following targets:

- blood pressure, 120/70
- fasting serum glucose, 115 mg/DL
- total cholesterol, 190 mg/DL
- smoking, no

Patients with vascular risk factor measures outside the targets are returned to primary care with a written request for more aggressive therapy. We remeasure the risk factors at subsequent clinical visits.

Cognitive-Enhancing Medications

For patients with probable AD in accordance with NINCDS Criteria, we prescribe a cholinesterase inhibitor, followed by the addition of memantine three months later. We allow the prescription of such medications for amnestic Mild Cognitive Impairment patients, at provider discretion.

We plan to document the clinical results of all our therapeutic interventions, leveraging the tools of Cleveland Clinic Neurological Institute’s Knowledge Program, a clinical data archival project that we are systematically using to analyze patient care and improve outcomes.

A Treatable Disease

The multimodal approach to Alzheimer’s disease and its spectrum disorders, outlined above, is just a beginning. With its establishment, we are saying that Alzheimer’s disease must be considered a treatable disorder; that we must begin to apply the neuroscience insights garnered over past years; and that we must subject our treatment approaches to constant revision as new evidence emerges.

In time, we will turn our efforts to prevention for those at special risk for development of Alzheimer’s disease. With our clinical program, we will integrate translational research into the causes, diagnosis and treatment of AD. We will constantly attempt to move our interventions into earlier stages in the presentation of the disease. At the Cleveland Clinic Lou Ruvo Center for Brain Health, we are dedicating ourselves to this great undertaking, and we will not rest until real progress has been made.

Randolph B. Schiffer, MD, is Director of Cleveland Clinic’s Lou Ruvo Center for Brain Health. His specialty interests include neurocognitive disorders such as Alzheimer’s disease, multiple sclerosis and neuropsychiatric disease. He can be contacted at 216.445.7132 or schiffer@ccf.org.

REFERENCES


Using Functional Magnetic Resonance Imaging to Detect Early Changes in Brain Activation Patterns in Alzheimer’s Disease

By Stephen Rao, PhD, ABPP-CN

By the time Alzheimer’s disease (AD) becomes symptomatic, it has caused brain changes that make it more difficult to treat. If the disease could be detected and treated at a preclinical stage, its onset could be delayed and its prevalence significantly reduced. Research at Cleveland Clinic Neurological Institute has found that functional magnetic resonance imaging (fMRI) can detect the earliest brain changes associated with the disease in asymptomatic, at-risk individuals. The goal of upcoming research is to use this imaging technology to assess the efficacy of drugs in delaying onset of the disease.

Alzheimer’s disease affects an estimated 5 million Americans, mostly over age 60. As the senior population grows, the incidence rate is expected to double every 20 years. With Medicare spending for AD estimated at $1.1 trillion in 2005, future social and financial costs could overwhelm family and public resources.

By the time individuals are diagnosed, they have likely been developing the disease for a decade or longer and have sustained fairly significant memory loss and some brain atrophy. Current treatments are limited in their ability to arrest symptoms and improve quality of life during the eight to 10 years that patients typically survive after diagnosis. It is estimated that a five-year delay in AD onset would decrease prevalence by 50 percent and a 10-year delay would make the disease virtually non-existent. Thus, delaying onset has become the major focus of Alzheimer’s disease research.

fMRI as a Biomarker

The preclinical stage is characterized by two phases: the latent phase, with no observable clinical symptoms, and the prodromal phase, known as Mild Cognitive Impairment (MCI), in which progressive clinical symptoms restricted to one cognitive domain, such as memory, appear. Every year, 10 percent of MCI patients develop AD, with 50 percent afflicted in five years. Treatment with effective therapies at this stage could go a long way toward reducing incidence of AD.

To reach this goal, a biomarker (or combination of biomarkers) is needed that can detect the earliest brain changes associated with the disease, predict future decline and measure treatment response. One approach is biochemical analysis of cerebrospinal fluid (CSF) protein, but that requires a lumbar puncture. Serial lumbar punctures limit the potential clinical utility of CSF biomarkers. Another approach is to use imaging as a marker. A research project, funded by the National Institute of Aging beginning in May 2003, evaluated fMRI as a potential biomarker, utilizing it to measure brain activation in healthy individuals at risk for developing Alzheimer’s disease and in MCI patients.

The first phase of the study evaluated three groups of older participants: 30 individuals with one or two APOE ε4 risk-factor genes and a positive family history of dementia; 30 individuals without the gene but with a family history of dementia; and 30 individuals with no risk factors (controls). In one key experiment, participants first underwent neuropsychological testing, then took a semantic memory test to discriminate names of famous people from those of unfamiliar persons while undergoing fMRI. Earlier research had shown that the memory test activated the first regions of the brain affected by AD (medial temporal lobe, precuneus/posterior cingulate and temporoparietal junction).

There were no significant differences among the groups in their neuropsychological test scores or memory test performance. The two at-risk groups, however, exhibited a pattern of hyperactivation on the fMRI scanning that was not observed in the control group. The fMRI hyperactivation is thought to result from a compensatory response in which the brain “works harder” to enable the person at risk to perform at a normal level. This finding suggests that fMRI can detect brain function anomalies in asymptomatic, at-risk individuals who do not exhibit signs of brain atrophy.
To assess longitudinal changes in semantic memory activation, the same cognitively intact participants were retested after a 1.5-year interval. In analyzing the results, we were able to identify those participants who would eventually show cognitive decline based on their baseline fMRI study. Cognitive decline was not predicted by risk factors, demographic variables or atrophy of the hippocampus.

Over the course of the project, additional experiments included amnestic MCI (aMCI) patients. When 19 aMCI patients, 19 at-risk subjects and 19 not-at-risk participants were administered the memory task with fMRI, the aMCI patients showed the greatest brain activation, despite test performance that did not differ significantly from that of the healthy groups. Retested at 1.5 years, participants with declining cognitive performance showed increasing levels of brain activation.

**Assessing Treatment Response**

We analyzed data from the above two experiments to determine whether cholinesterase inhibitors, the class of drugs commonly used to treat AD, affect cognitive functioning in aMCI patients. We identified eight aMCI patients who had been taking rivastigmine and donepezil at baseline and throughout the 18-month follow-up period. The treated patients showed a reduction (i.e., normalization) in task-activated fMRI magnitude compared with untreated patients (Figure 1). The changes in fMRI magnitude showed greater sensitivity to treatment response than the neuropsychological tests showed, further validating fMRI’s effectiveness as a biomarker.

The next phase of this research project, currently awaiting National Institutes of Health approval, will include a 24-week, randomized, double-blind, placebo-controlled parallel group study of the rivastigmine transdermal patch in 120 aMCI patients who have one or both APOE ε4 risk-factor genes. The study will compare fMRI to neuropsychological testing and structural MRI in detecting treatment response at 24 weeks.

The project will also involve continued longitudinal testing (at 5.5 and 7.0 years) of the three groups of aMCI, at-risk and not-at-risk participants to determine whether fMRI activation increases over time in at-risk participants and whether baseline fMRI activation patterns continue to predict participants who eventually become symptomatic.

This line of research shows promise in advancing the long-term goal of establishing fMRI as an effective biomarker for clinical trials to test medications that can delay onset in asymptomatic, at-risk individuals.

**Suggested Reading**

First-in-Man Study Evaluates Laser Interstitial Thermal Therapy for Inoperable Brain Tumors

By Gene Barnett, MD, FACS

Laser interstitial thermal therapy (LITT) for the treatment of cancer is not a new technique. The technology used to deliver the laser energy and monitor the tissue damage has been quite rudimentary, however, and these deficiencies have limited the adoption of this modality as a viable treatment for brain tumors. A new system (AutoLITT™, Monteris Medical) features several technological improvements that address these issues. Cleveland Clinic’s Brain Tumor and Neuro-Oncology Center was first in the world to test this platform in humans, and the results demonstrated proof of concept and provided preliminary safety and efficacy data.

Currently, the Brain Tumor and Neuro-Oncology Center is participating in a two-center, Phase I, first-in-man study investigating this system in patients with suspected recurrent or progressive glioblastoma tumors. Enrollment is still ongoing, but initial experience in the first several patients suggests that this technology holds promise for changing the landscape of neurosurgery for both benign and malignant brain tumors by providing an opportunity to treat previously inoperable tumors using a minimally invasive technique.

**Improved Technology**

The innovations of the AutoLITT™ system involve both the probe design and the monitoring technique. Rather than a bare fiber, the laser probe is housed in a special sheath that both provides cooling and emits the laser energy radially. Cooling prevents tissue charring, which would block effective transmission of the laser energy. Unidirectional firing of the laser sideways through the probe results in more focused delivery of the energy to enable targeting of irregularly shaped tumors while sparing surrounding normal tissue.

The system also features steering technology so that the surgeon can remotely control the direction of the laser probe and its depth in the brain. In addition, it offers feedback control to achieve conformal heating using real-time magnetic resonance thermometry combined with a proprietary algorithm to predict thermal tissue damage. The algorithm is based on the Arrhenius equation that determines the likelihood of irreversible cell death using temperature and time data. The laser and 1.5 T MR scanner are interfaced to a computer workstation, and at intervals of about five seconds, the monitor refreshes to display boundary lines encompassing three tissue regions representing 100 percent safety, intermediate safety and 100 percent cell kill.

**Thermal Therapy**

The main purpose of the Phase I study is to evaluate the safety of the LITT system, so the primary outcome measure is being determined by absence of severe clinical toxicity or procedure-related neurological deficits. The methodology involves thermal dose escalation, such that once the safety of an initial treatment protocol is established, subsequently enrolled patients are treated with approaches that are progressively more aggressive in terms of the targeted area of tissue kill. Initially, patients were treated only until the 100 percent safe boundary line reached the outer edge of the tumor. Now, we have moved ahead to where treatment is continued until the intermediate safety line matches the tumor border and, if that approach proves safe, treatment will be delivered until the 100 percent cell kill line encompasses the entire tumor.

Only a handful of patients have been treated to date, but no patient suffered an unexpected serious complication. Encouragingly, in all cases the thermal therapy has been effective in destroying a substantial portion of the tumor as assessed by post-treatment MRI-detected tissue necrosis.

**A Minimally Invasive Option**

In May 2009, the AutoLITT system received clearance from the Food and Drug Administration for use in neurosurgery. Looking ahead, we believe there is great potential for this intervention to be further improved
Intraoperative imaging of first-ever treatment of human brain tumor (glioblastoma) using the AutoLITT™ thermal therapy system.

and expanded. For example, methodologies are being developed that will allow treatment by multiple trajectories, thereby allowing for more complete treatment of even larger tumors.

In our own center, we look forward to the opening this year of a high-field MRI interventional suite. Placement of the guidance device and the MRI-guided treatment will be completed in a single room, without necessitating patient transport from the operating room to the radiology department.

We also anticipate that this minimally invasive technique will become an option for treating a much broader array of tumor types, including benign as well as other malignant lesions, so that the potential therapeutic benefit of open surgery can be extended to more patients with brain tumors that cannot be reached readily or safely through open surgery.

Gene Barnett, MD, FACS, holds the Rose Ella Burkhardt Chair in Neurosurgical Oncology and is Director of the Brain Tumor and Neuro-Oncology Center at Cleveland Clinic. His specialty interests include benign and malignant tumors of the brain and spinal cord, Gamma Knife® radiosurgery and brain metastases. He can be contacted at 216.444.5381 or barnetg@ccf.org.

Additional Brain Tumor Research

Stem Cells and Regenerative Medicine

In the Department of Stem Cell Biology and Regenerative Medicine at Cleveland Clinic Lerner Research Institute, Jeremy Rich, MD, is researching cancer stem cells in brain tumors and novel treatments aimed at slowing brain tumor growth:

Tumors are aberrant organ systems containing a complex interplay between the neoplastic compartment and recruited vascular, inflammatory and stromal elements. Further, most cancers display a hierarchy of differentiation states within the tumor cells. Molecular signals that drive tumor formation and maintenance commonly overlap with those involved in normal development and wound responses — two processes in which normal stem cells function. Therefore, it is not surprising that cancers invokes stem cell programs that promote tumor malignancy.

We have defined roles for cancer stem cells in radiation resistance and tumor angiogenesis, suggesting that cancer stem cells are useful therapeutic targets. Based on these findings, we have interrogated a wide array of molecular targets that may contribute to cancer stem cells. We have identified several molecular targets that offer promise, as some may be directly targetable. Like somatic stem cells, cancer stem cells reside in specific niches (perivascular and hypoxic), and nonstem cells may be reprogrammed toward a stem cell state through microenvironmental conditions. These studies may translate into improved diagnostic, prognostic and therapeutic approaches for these lethal cancers.

Targeting Angiogenesis in Glioblastoma Tumors

In the Department of Cancer Biology at Cleveland Clinic Lerner Research Institute, Candece Gladson, MD, is focusing on the development of new anti-angiogenic agents for malignant glioma tumors:

Anti-angiogenic therapy is a promising strategy for treatment of glioblastoma and other malignant glioma tumors, due to the extensive neovasculature associated with these tumors. The effective application of anti-angiogenic therapy is complicated, however, by the tumors’ location, which requires development of novel methods to monitor response and assess recurrence; the current lack of anti-angiogenic therapies that eliminate the extensive neovasculature associated with brain tumors, rather than causing normalization of the blood vessels; and the possibility that these tumors will recur with a more aggressive phenotype.

This work is laying the basis for clinical trials designed to evaluate the optimal timing of administration of these agents, in combination with other treatment modalities in patients with these tumors.

For additional information on these research projects, contact Jeremy Rich, MD, at richj@ccf.org or Candece Gladson, MD, at gladso@ccf.org.
Cerebrospinal Fluid Neutrophil Percentage as a Predictor of Vasospasm after Subarachnoid Hemorrhage

By J. Javier Provencio, MD, FCCM

Cerebral vasospasm (CV) is a significant cause of morbidity in patients with aneurysmal subarachnoid hemorrhage (SAH). CV develops in about 40 percent of patients five to 12 days after the rupture and causes narrowing of cerebral blood vessels. In cases of severe ischemia, CV can result in irreversible focal neurological deficits, infarction, coma and death. Therapeutic options for CV are limited. A more effective approach would be to identify patients at risk for CV and apply preventive measures. Based on our research, we believe cerebrospinal fluid (CSF) neutrophil percentage is a predictor of CV risk post-SAH. The ability to predict CV risk opens the door for new interventional strategies. More importantly, understanding the mechanism of CV may lead to more effective treatments.

Evidence for Neutrophil Involvement

Although the pathogenesis of CV has been studied for some 60 years, the exact mechanism has remained elusive. Evidence is accumulating, however, that the inflammatory response accompanying SAH is responsible for CV, and recent studies suggest a direct pathogenic role for neutrophils in CV following SAH.

Upregulation of cell adhesion molecules on endothelial cells following aneurysmal SAH leads to migration of neutrophils into the subarachnoid space. Once on location, these neutrophils can initiate cellular processes capable of causing the vascular effects observed in CV. Notably, neutrophils directly produce several reactive oxygen species (ROS) such as superoxide and hypochlorite.

Evidence for neutrophil involvement in CV comes from animal models in which blocking e-selectin, which is needed for leukocyte entry into the central nervous system, and administering antibodies against the neutrophil/macrophage adhesion molecule CD11/CD18 decreased CV severity.

Neutrophils in Cerebrospinal Fluid

Based on studies demonstrating a possible pathogenic role for neutrophils in CV after aneurysmal SAH, the aim of our study was to determine whether neutrophil levels in the CSF were predictive of CV risk.

We began with a retrospective analysis of laboratory data from CSF samples from 36 patients with SAH and external ventricular drainage devices (EVDs), collected at our institution between 2000 and 2002. Ten of the 36 patients (28 percent) developed CV. We found no significant differences in red blood cells (RBCs), total leukocytes (WBCs), WBC/RBC ratio or the percentage of CSF leukocytes represented by lymphocytes, monocytes or eosinophils between patients with and without CV; however, the median percentage of CSF leukocytes represented by neutrophils (CSF neutrophil percentage) on the third day post-hemorrhage was significantly greater in patients who developed CV compared with patients who did not (73 percent [66-90] vs. 51 percent [29-72]).

These data strongly suggested that intrathecal neutrophil accumulation was associated with CV after SAH. To test this hypothesis, we next conducted a prospective study using a similar cohort of 34 patients treated at Cleveland Clinic between 2004 and 2008.

Consistent with the retrospective study, we found no difference between CV and non-CV patients in total RBCs, WBCs, WBC/RBC ratio, or percentage of lymphocytes and monocytes. Again, the CSF neutrophil percentage increased significantly in the group of patients who went on to develop CV compared with those who did not develop CV.

In a subsequent animal model, we found that depletion of neutrophils ameliorated vasospasm after SAH. This finding supports our hypothesis that neutrophils, more than being just a marker of CV, are important in the pathogenesis of CV.
Level and Day Both Critical

To further refine these findings in patients, we analyzed the combined data from both cohorts to attempt to identify a critical CSF neutrophil percentage for CV risk. We determined that a neutrophil percentage of 62 percent or greater identified patients at risk for CV. Neutrophil percentage had superior predictive value compared with the two other commonly used predictors for CV (the Hunt and Hess Grade and the Fisher CT Grade).

Although it seems curious that neutrophil percentage on Day 3 is a significant predictor while on other days it is nondiscriminatory, the explanation for this phenomenon may be straightforward. During the first two days post-SAH, the neutrophilic inflammation is developing, and neutrophil levels have not yet reached the critical stage. Subsequent to Day 3, neutrophil levels increase in all patients with EVDs (standard treatment for SAH), possibly as part of a foreign body response. Therefore, the time frame in which neutrophil percentage is predictive of CV risk is fleeting.

Clinical Application

Thus, the therapeutic window of opportunity is narrow. With the goal of preventing CV and subsequent permanent neurologic deficits, treatment must be initiated between Day 3, when CSF neutrophils become elevated, and Days 5 to 12, when symptoms of CV typically develop.

In clinical use, application of neutrophil percentage as a predictor for CV should be limited to SAH patients with EVDs (the conditions of the study). Another limitation to the application of these findings is the lack of reliability of neutrophil percentage when there are very few cells to count (<10 WBC/μl), which occurs in approximately 10 percent of patients.

Although we have demonstrated the accumulation of neutrophils in CSF in association with CV in patients, and a causative link with neutrophils in an animal model, further research is needed to elucidate their exact role in the ischemic events. We hope that a better understanding of these mechanisms will lead to new, more targeted interventions that can decrease the incidence of CV and its associated morbidity.

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The Stereo-EEG Technique for Treatment of Refractory Epilepsy

By Jorge Gonzalez-Martinez, MD, PhD

For patients with complex, intractable focal epilepsy, the monitoring technique known as stereoelectroencephalography (SEEG) offers the prospect of treatment options previously foreclosed to them, including surgical intervention. With the March 2009 initiation of the first SEEG program in North America at Cleveland Clinic’s Epilepsy Center, we are expanding our capabilities to target the epileptogenic zone in these patients less invasively and with much greater precision.

During the last 50 years, epilepsy surgery has benefited from modern neuroimaging and other noninvasive localizing techniques that have improved the safety, accuracy and efficacy of pre-surgical investigations and surgical treatment. Refinement of these techniques, as well as increasing experience with the pre-surgical evaluation of patients with drug-resistant focal epilepsies, has significantly decreased the number of cases requiring invasive intracranial electroencephalography (EEG) recording.

Nevertheless, in a considerable number of patients, noninvasive investigations fail to localize the site of origin and early spread of the ictal discharge, also known as the epileptogenic zone. Furthermore, if highly eloquent areas are suspected of involvement in the ictal discharge, functional mapping is mandatory when planning resective surgery close to these regions to avoid new, unwanted postoperative permanent neurological deficits. For these reasons, invasive intracranial EEG recording is still indicated in selected patients.

Various techniques for intracranial EEG recording are currently used, and each has its advantages and drawbacks. Chronically implanted subdural electrodes allow recording from large superficial cortical areas, but they provide limited coverage of deep-seated structures such as the hippocampus, deep mesial structures such as the cingulate gyrus and the posterior orbito-frontal areas, or the cortex within the sulci. Intracerebral electrodes have the advantage of an excellent sampling from mesial structures and from the intrasulcal cortex, with the disadvantage of providing information from a limited volume of tissue. Combined use of subdural and depth electrodes has been advocated and implemented at Cleveland Clinic. The lack of stereotactic precision and the continuing need for larger craniotomies represent important limitations to this approach.

Stereotaxy and Focal Epilepsy Surgery

Stereotactic methods are closely associated with surgery of subcortical nuclei to treat movement disorders, chronic pain and depression. However, over the past 60 years, the application of stereotactic investigation prior to surgery for focal epilepsy, especially in the localization of cortical epileptogenic foci, has gradually enlarged the field of stereotactic techniques, first to the temporal lobe (Talaraich et al., 1958) and then to the whole cerebral cortex (Bancaud et al., 1965).

Today, chronic intracranial EEG monitoring with stereotactically implanted intracerebral electrodes is a standard technique in Europe, with proven safety and effectiveness. At major epilepsy centers across that continent, approximately 45 percent of resective surgical procedures in patients with drug-resistant focal epilepsy are performed after use of this invasive method of investigation.

Of course, the introduction of intracerebral electrodes as well as interpretation of the recorded data necessitate detailed localization of the structures investigated and precise knowledge of their vascular supply, the latter for the obvious reason of safety during surgical implantation of the depth electrodes. The need for precision and safety prompted development of stereo-tele-angiographic techniques by Talaraich and Sziklai in the late 1960s. These methods are still used in many centers in Europe. Recent progress in neuroradiology, such as 3D angiography, MRI and the possibility of imaging fusion using commercially available neuronavigation software, revolutionized the planning of stereotactic trajectories for SEEG (Figure 1).
Targeting the Epileptogenic Zone

SEEG methodology implies a rigorous pre-implantation scrutiny of all available findings obtained during the noninvasive phase to define a coherent hypothesis of the likelihood of localization of the epileptogenic zone. In this decision-making process, the respective weight of MRI, interictal/ictal EEG and ictal clinical characteristics may vary greatly, depending on the patient.

After a localizing hypothesis is formulated, a tailored implantation strategy is planned, with the goal of confirming or rejecting the hypothesis. In this phase, the exploration is focused to sample the anatomic lesion (if present), the more likely structure(s) of ictal onset and the possible pathway(s) of propagation of the discharge. The desired targets then are reached with the precision of the stereotactic technique, allowing them to be recorded from lateral, intermediate or deep structures in a three-dimensional arrangement, thus accounting for the dynamic, multidirectional spatiotemporal organization of the ictal discharge (Figure 2).

On these grounds, SEEG differs substantially from depth recording, which relies on bilateral and symmetrical placement of intracerebral electrodes in standardized anatomic targets, on the assumption that one should avoid biasing the exploration strategy in favor of one’s preferred localizing hypothesis. With these methodological premises, SEEG, while offering the advantages of a stereotactic, three-dimensional concept of the ictal discharge, has the disadvantage of tunnel vision, as opposed to subdural arrays, which allow one to follow development of the epileptic discharge over the surface of a large portion of the cerebral cortex.

A judicious combination of stereotactically implanted intracerebral electrodes and subdural grids may be a helpful option for patients with highly complex, intractable focal epilepsy, who until now have been left with no hope of further clinical or surgical approaches for their debilitating recurrent seizures.

Suggested Reading


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Testing Targets Oral Treatments for Multiple Sclerosis

By Jeffrey Cohen, MD

Treatment of multiple sclerosis (MS) is on the threshold of a new era of better disease management and enhanced patient comfort through the development of several promising oral medications.

Despite the availability of a half-dozen disease-modifying drugs, development of an effective oral drug has long been the Holy Grail in MS research. Currently approved treatments, delivered by infusion or subcutaneous or intramuscular injection, have been the best available for almost two decades, yet the standard agents reduce relapse rates by only about 30 percent. Additionally, long-term compliance often is compromised by patient pain, anxiety, inconvenience and localized reactions at the injection site.

Finally, our understanding of the MS disease process has progressed to the point where novel classes of drugs hold the promise of the long-awaited breakthrough. Neurologists at Cleveland Clinic’s Mellen Center for Multiple Sclerosis Treatment and Research — who played lead roles in developing currently approved therapies for MS such as interferon beta 1-a, glatiramer acetate and natalizumab — are closely involved in research related to several new oral agents, which are now in Phase III testing.

Clinical Trials

MS is thought to be a lymphocyte-dependent autoimmune disorder. That underlying pathology explains the results achieved with oral cladribine, a lymphotoxic agent approved for hematological malignancies, in the Phase III CLARITY study. As reported this past January, cladribine significantly reduced the relapse rate compared with placebo, leading the Food and Drug Administration (FDA) to assign the drug fast-track status.

The ORACLE trial, which opened in October 2008, will compare two dosage regimens of oral cladribine vs. placebo in subjects who have had a first clinical demyelinating event and have brain scans suggestive of MS. The study period will be two years, or to the time when a patient experiences a second event that leads to a diagnosis of clinical MS. Those patients will be offered treatment with interferon beta 1-a (Rebif®) for two years. Patients who do not convert to clinically definite MS within the study period will be offered an additional two-year follow-up treatment period with oral cladribine.

The study aims to evaluate the effects of initiating treatment with a disease-modifying drug at the earliest stage on slowing or preventing irreversible neurologic damage and delaying the development of MS.

Fingolimod (FTY720) alters lymphocyte trafficking to reduce abnormal inflammation in the nervous system in MS. In the TRANSFORMS Phase III trial of fingolimod in 1,292 patients worldwide, the study drug significantly reduced relapses compared with interferon beta-1a (Avonex®). The annualized relapse rate at one year was 0.16 for patients taking a 0.5 mg daily dose and 0.20 for patients taking a 1.25 mg daily dose, a 52 percent and 38 percent reduction, respectively, vs. interferon beta-1a. The difference in relapse rate between the two doses of fingolimod was not significant. Comprehensive data analysis is ongoing.

Two additional pivotal studies of fingolimod — FREEDOMS and FREEDOMS II — will be completed this year. These two-year, placebo-controlled studies are expected to add data in support of fingolimod’s efficacy in reducing relapse frequency and slowing the progression of disability.

Mellen Center Medical Director Robert Fox, MD, is Principal Investigator on the CONFIRM trial, a Phase III study of the oral immunomodulator fumarate (BG12). A total of 1,232 patients at 175 sites worldwide will be randomized to low-dose fumarate, high-dose fumarate, glatiramer acetate (COPAXONE®) or placebo for the two-year study.
Along with clinical assessments, quantitative analyses of MRI-detected lesions and brain atrophy are utilized in MS clinical trials to monitor disease activity and progression.

CONFIRM and DEFINE, another ongoing Phase III trial, follow a Phase Ib trial of fumarate involving 257 patients that was published last year. In this trial, patients taking fumarate, 240 mg three times daily, had 69 percent fewer new gadolinium-enhancing lesions on MRI compared with placebo ($P < 0.0001$). Researchers speculate that fumarate has both neuroprotective and anti-inflammatory effects.

The Mellen Center also is involved in the BRAVO Phase III trial of the oral immunomodulator laquinimod. In a Phase II study published last fall, a 0.60 mg daily dose of laquinimod reduced disease activity on MRI by an average 51 percent compared with placebo. Additionally, the study showed a favorable trend toward reduced annual relapse rates and in the number of relapse-free patients compared with placebo.

ALLEGRO, the first of the Phase III laquinimod trials, closed enrollment at 1,000 patients in November 2008, while BRAVO currently is enrolling patients to reach the goal of 1,200 participants. In February 2009, laquinimod became the second oral MS drug to be granted fast-track status by the FDA.

**Expanding Treatment Options**

In addition to these agents, the development pipeline for oral MS therapy includes several drugs in earlier stages of evaluation. Some of the more promising agents, which act through a variety of mechanisms, include statins (cholesterol-lowering agents that also appear to have immunologic effects), estril (a hormone that plays a role in the immunologic effects of pregnancy) and minocycline (an antibiotic that has immune effects).

Treatment options for MS are expected to expand over the next several years as oral drugs are granted FDA approval and become widely available. Additional research is needed, however, to delineate their risk-benefit profiles to assist the neurologist in deciding which medication is most appropriate for each patient.
An Interdisciplinary Approach to Treatment of Chronic Nonmalignant Pain

By Edward Covington, MD, and Judith Scheman, PhD

Many patients with chronic nonmalignant pain fail to achieve reasonable comfort and function despite appropriate treatment with single or even several therapies. Interdisciplinary pain rehabilitation programs (IPRPs) typically combine many treatments into programs that range from a few hours a week to inpatient in intensity. It seems a truism in medicine that the more treatments that have failed, the less the likelihood the next one will succeed. Despite this, and the fact that IPRPs typically treat only patients who have failed multiple single interventions, their success rate is high.

Early IPRPs were based largely on Fordyce’s behavioral approach, which emphasized operant conditioning and exercises. Although methods have evolved, there remains in most programs a focus on replacing sick role type behaviors with normal activities, which staff attempts to reinforce.

Targets for IPRP treatment include not only pain, but also function, mood (depression, anger and anxiety), inappropriate healthcare utilization and comorbid psychiatric illness. While programs differ, common elements typically include:

- education
- physical reconditioning
- biofeedback and relaxation training
- pharmacotherapy
- psychotherapies: individual, group, family
- treatment of psychiatric comorbidity, including addiction
- drug weaning

Some programs provide such interventional treatments as epidural steroids and trigger point injections. Some offer massage/myofascial release, yoga and martial arts exercises.

Improved Outcomes

In a review of outcome studies, Turk found that patients in IPRPs experience pain reduction ranging from 14 to 60 percent, decrease in opioid use up to 73 percent, dramatic increases in activity levels, a 90 percent reduction in physician visits (one study), 50 to 65 percent fewer surgeries and 65 percent fewer hospitalizations than untreated patients undergo. Additionally, 43 percent more patients work after IPRP treatment than before (twice the untreated rate) and 35 percent fewer receive disability income.¹

Deardorff’s review found pain reductions of 14 to 42 percent and improvements in physical reconditioning. Forty-nine percent had reduced narcotics use and 65 percent were drug free at one year. Healthcare utilization was reduced, and 47 to 90 percent were seeking no additional care at one year. Work/vocational rehabilitation was successful in 55 percent. Treatment results were usually maintained at 2.5 to 3 years.²

In a meta-analysis of 65 studies of IPRPs, Flor et al. found improvements in pain, mood and interference with life activities, including work.³ Healthcare utilization declined. Benefits were stable over time; however, most studies were of marginal quality. Blinding and obtaining appropriate control groups have been problematic in this research.

Turk compared costs of returning a patient to work with various treatments, including drugs, conservative care, surgery, spinal cord stimulation, implantable drug delivery systems and pain rehabilitation programs. He found that IPRPs led to comparable pain reduction, but superior outcomes in terms of medication use, healthcare utilization, functional activities, return to work, closure of disability claims, iatrogenic consequences and adverse events.⁴ Using 1995 dollars, he found 27 fewer surgeries per 100 patients leading to $4,050 saved per patient (at $15,000 per operation). Annual medical costs,
which averaged more than $13,000 a year pretreatment, dropped to $5,600 in the year after treatment, leading to $7,700 a year saved per patient. This savings was in addition to $400,000 saved per person removed from permanent disability.

In 2009 evidence-based guidelines for the treatment of low back pain, Chou et al. concluded that interdisciplinary chronic pain rehabilitation was moderately superior to non-interdisciplinary rehabilitation or usual care for improving functional status. It was also found to be as effective as surgical fusion in patients willing and able to commit the time and effort necessary for rehabilitation.

A 13-year follow-up study by Patrick et al. of patients who had participated in an IPRP showed that patients maintained gains in pain relief, mood and function, lending support for the long-term efficacy of this form of treatment.

A systematic review of the efficacy of IPRPs by Guzmán et al. concluded that “intensive multidisciplinary biopsychosocial rehabilitation with functional restoration reduces pain and improves function in patients with chronic low back pain. Less intensive interventions did not show improvements in clinically relevant outcomes.”

In a comprehensive review of studies examining the efficacy and cost effectiveness of IPRPs, Gatchel and Okifuji found the programs were “the most efficacious and cost-effective treatment for persons with chronic pain, relative to a host of widely used conventional medical treatments.”

It is reasonable to conclude that when “everything has failed,” many patients can be restored to good function and quality of life with IPRP treatment. Unfortunately, many such programs have ceased to exist due to poor reimbursement.

**Comprehensive Care**

Cleveland Clinic’s Chronic Pain Rehabilitation Program (CPRP) is a three- to four-week intensive outpatient interdisciplinary program that targets pain, functional impairment, mood and overall suffering in patients with disabling chronic pain. The number of patients graduating from the program annually has generally increased, from 146 in 2004 to 240 in 2009 (annualized).

In treatment, patients are helped to accept that there is no complete cure for chronic pain, but that it need
Debility based on inordinate fear of reinjury (so-called kinesiophobia) is reversed with work in the gym and psychotherapy. This fear immobilizes many patients with chronic pain. Catastrophic thinking, which has been compellingly shown to worsen suffering and disability, responds to the desensitization of graded exercises and relaxation training. These issues demonstrate the close integration of disciplines, in which physical therapy helps psychiatric status and psychotherapy facilitates exercises. It is at this interface between psyche and soma where much progress in the program is made.

Most patients in the CPRP have failed to achieve sustained benefit from high-dose opioids, which are therefore weaned. Others maintain some benefit and are continued on opioids, usually at low doses. Aggressive use is made of the adjuvant analgesics, primarily selected antidepressants and anti-epileptic drugs.

Addressing Substance Abuse

More than 30 percent of patients treated in the CPRP also have an active substance use disorder. We have found that for treatment to be successful, both these problems must be addressed. Failure to treat one leads to failure in treating the other. Therefore, our team includes a full-time chemical dependence counselor and several other staff with training in this field. When indicated, patients receive a substance abuse evaluation, and treatment is started while they are in the program. Although patients with addictive disorders tend to drop out of treatment somewhat more often than those without this illness, we find that those who complete treatment improve as much as those without substance abuse issues.

Measurement

Our patients participate in the following program components:

- physical therapy/occupational therapy
- psychophysiological training/stress management

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<th>Mean Depression Anxiety Stress Scale Scores</th>
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<td>1-Year Follow-Up</td>
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Figure 3: In 2006, the CPRP adopted the Depression Anxiety Stress Scale (DASS) for assessment of patient mood pre- and post-treatment. In the period indicated, mean DASS scores for depression improved from moderate at admission to normal at discharge. Mean scores for anxiety improved from moderate at admission to mild at discharge, and preliminary 2008 follow-up data show anxiety as normalized at six months.

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<th>Mean PDI Scores at Admission and Discharge</th>
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Figure 4: The Pain Disability Index (PDI) measures patients’ perceived disability due to pain in seven domains. Patients score their disability on a scale of 0 (no disability) to 10 (total disability). On admission, CPRP patients report moderate to severe disability in all seven domains. By discharge, these scores have normalized, meaning that patients no longer see their functioning impaired by pain.
• pain education
• individual and group therapy, including cognitive behavioral therapy and dynamic group therapy
• couples/family therapy
• anger management
• assertiveness training
• medication management, including weaning from opioids and benzodiazepines when needed
• addiction evaluation and counseling, as needed
• aftercare treatment (available once a month)

Outcome data are collected on all patients admitted to the program as part of an IRB-approved data registry. A number of variables are collected, including measures of pain intensity, disability due to pain, and depression. These data are used both for monitoring treatment quality and for scientific studies.

Our outcome studies demonstrate that patients weaned from high-dose opioids (mean 455 mg/d morphine equivalents) experience a paradoxical reduction in pain. Additionally, these patients demonstrate improved cognitive function over the course of treatment. Follow-up studies demonstrate that this benefit is maintained at one year, and a previous long-term study showed benefit maintained at three years.

We cannot definitively explain why chronic pain interventions that fail in isolation are effective in combination, but the literature and our experience demonstrate that a coordinated interdisciplinary approach offers the greatest opportunity for success with members of the population who fail or are not candidates for other forms of care.

REFERENCES


Edward Covington, MD, is the founder of the Chronic Pain Rehabilitation Program and Director of the Neurological Center for Pain at Cleveland Clinic. His specialty interests include chronic pain and pain management. He can be contacted at 216.444.5964 or covinge@ccf.org.

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A Novel Approach toward Elucidating the Pathophysiology of Dystonia

By Jerrold L. Vitek, MD, PhD, and Jay L. Alberts, PhD

Deep brain stimulation (DBS) of the internal segment of the globus pallidus (GPI) has emerged as an effective neurosurgical treatment option for both generalized and focal dystonia. The optimal site for lead placement within the GPI and choice of stimulation parameters, however, have not been defined. Complicating matters further is the fact that onset of a clinical response following stimulation may not occur for days, weeks or even months.

The delay in improvement of symptoms following onset of stimulation or a change in stimulation parameters delays the time between stimulator adjustments. As a result, it may take up to one year for the multiple return visits needed to optimize the stimulation parameters. A better understanding of the pathophysiology and functional organization of GPI in dystonia would help physicians choose the site of lead placement and predetermine stimulation parameters that would optimize clinical outcome.

Absence of a good animal model of dystonia has been an important factor in the lack of understanding of the pathophysiology of this movement disorder and the mechanism of action of DBS in dystonia. The microelectrode-guided lead placement approach used in pallidal DBS surgery, however, provides a means to study the physiological characteristics of GPI neurons in affected patients. At Cleveland Clinic Neurological Institute’s Center for Neurological Restoration, we are taking advantage of this opportunity, combined with the broad-ranging expertise offered by our interdisciplinary team, to embark on a novel investigation that may provide groundbreaking information on the pathophysiology of dystonia and offer insight for future improvements in its surgical treatment.

**Correlating Neuronal and Muscle Activity**

Our study involves the simultaneous recording of neuronal activity in the GPI, muscle activity and force control data. To our knowledge, it represents the first time that biomechanical measures of motor performance will be collected concurrently with neuronal activity in patients with primary dystonia.

The study will enroll patients with generalized or cervical dystonia who have elected to receive treatment with DBS. Our specific aims are to determine the physiological characteristics of neurons in the basal ganglia of patients with dystonia, whether the physiological characteristics correlate with clinical measures of dystonia severity, and if the anatomic distribution and proportion of abnormal neurons in the GPI differ between patients with generalized and cervical dystonia.

At enrollment, the severity of disease will be quantified using standardized instruments: the Burke Fahn Marsden Dystonia Rating Scale for patients with generalized dystonia and the Toronto Western Spasmodic Torticollis Rating Scale for cervical dystonia patients. In the operating room, neuronal activity in the GPI recorded from a microelectrode will be collected to determine the physiological characteristics of these neurons, including mean discharge rate, the somatosensory response properties of individual cells, and the number of cells with bursting or power at low oscillatory frequencies. Specific impairments in control of motor forces and the development of off-axis forces will be assessed by having patients perform a force-tracking motor task that allows delineation of force focusing and scaling.

Correlating this quantitative information with the data from simultaneously collected microelectrode recordings and EMG-recorded activity of individual muscles will allow correlation of neuronal activity to the abnormal control of muscle activity that occurs in patients with dystonia. Using a force control task enables this correlation without the confounding variable of involuntary limb movements that occur during movement in these patients.
The microelectrode-guided lead placement approach used in pallidal DBS surgery provides a means to study the physiological characteristics of GPi neurons in affected patients.

Refining DBS Treatment

If the current project proves successful in identifying the specific neurophysiological characteristics associated with dystonia and the spatial segregation of neurons affected in generalized and cervical dystonia, we anticipate this information will enable a more rational and more efficient approach to treatment with DBS, including optimizing stimulation patterns, directing lead placement and, perhaps, even suggesting new lead configurations. For example, if the results of our study corroborate existing evidence that GPi neuronal discharge rates are relatively low in patients with dystonia, it will support a new programming paradigm using a frequency just high enough to override the baseline rate in dystonia patients, but low enough to translate into a benefit by increasing the interval between battery changes.

Determining that the distribution of abnormal neurons differs depending on which muscles are affected by dystonia would suggest a targeted approach to lead placement that would be based on the affected body part(s) and would provide better clinical outcomes. Using this approach, it may also be possible to identify subtle improvements in force control that occur during intraoperative test stimulation, which could be predictive of long-term outcome and provide an intraoperative measure to determine whether a lead is placed optimally prior to taking the patient out of the operating room.

As we move forward with this study, the next phase would involve collaborating with our colleague, Cameron C. McIntyre, PhD, in the Department of Biomedical Engineering, who has created a modeling technique to determine the area of neural tissue affected by a lead given its position and stimulation parameters. This next phase would explore the possibility of combining the information about lead location and the changes in neuronal activity that occur in dystonia with modeling that predicts the area of GPi affected by stimulation to define optimal stimulation parameters for individual patients. We envision this science-guided approach would address the current challenges of stimulator programming for DBS treatment of dystonia, perhaps even to the point where the implantation and programming steps might someday be completed as a one-stage procedure.

Jerrold L. Vitek, MD, PhD, holds the Edward F. and Barbara A. Bell Family Endowed Chair and is Director of the Neuromodulation Research Center at Cleveland Clinic. His specialty interests include medical and surgical treatment of movement disorders, including Parkinson disease, dystonia and tremor; mechanisms of DBS; pathophysiology of movement disorders; and new applications for DBS. He can be contacted at 216.445.0267 or vitekj@ccf.org.

Jay Alberts, PhD, is a researcher in the Department of Biomedical Engineering at Cleveland Clinic. His specialty interests include the effects of DBS on motor functions of Parkinson disease patients and the effects of unilateral DBS on bilateral motor function. He can be contacted at 216.445.3222 or albertj@ccf.org.
Diagnosing Neuromuscular Respiratory Dysfunction:

Ultrasound-Guided Electromyography of the Diaphragm

By Steven Shook, MD

Diaphragm weakness as a cause for respiratory insufficiency is not uncommon, and is usually in the differential diagnosis of any patient with acute or chronic shortness of breath.

Diagnostic tools used in the assessment of diaphragm weakness include inspiration under fluoroscopy (i.e., the “sniff test”), as well as upright and supine spirometry. These tests can provide supportive evidence of diaphragmatic dysfunction, but are hampered by the potential for false positive and false negative results.

Phrenic nerve conduction studies and needle electromyography of the diaphragm provide specific information about diaphragm physiology. However, standard techniques for electromyography of the diaphragm are limited by lack of visualization of the target muscle, technical challenges in patients with large body habitus and the risk of pneumothorax. At Cleveland Clinic’s Neuromuscular Center, we have found that use of ultrasound guidance facilitates localization of the diaphragm for needle placement, improving the accuracy and decreasing the risk of the procedure.

Causes of Neuromuscular Respiratory Dysfunction

Neuromuscular respiratory insufficiency can occur for a variety of reasons and in a number of clinical settings, including intensive care, postoperative and outpatient. In critical care patients, the cause of difficulty weaning from mechanical ventilation can be difficult to determine, but includes phrenic nerve involvement in critical illness neuropathy and Guillain-Barré syndrome. Although rare, iatrogenic phrenic neuropathy should also be considered in postoperative patients who have undergone cardiothoracic surgery, cardiac radiofrequency ablation, lung transplantation and neck surgery.

In the outpatient setting, respiratory symptoms of neuromuscular disease range from morning headaches suggestive of nocturnal hypoventilation to severe progressive exertional dyspnea. These symptoms can be present in patients with motor neuron disease (e.g., amyotrophic lateral sclerosis), cervical polyradiculopathies, neuralgic amyotrophy, traumatic polyradiculopathies, neuralgic amyotrophy, traumatic phrenic nerve injury, myasthenia gravis and Lambert-Eaton syndrome, as well as acquired and hereditary myopathies.

Electrodiagnostic Testing of Respiratory Dysfunction

Determining the precise cause of neuromuscular respiratory dysfunction often requires a multidisciplinary approach, including input from pulmonary/critical care and neuromuscular specialists, aided by the results of focused electrodiagnostic testing.

Phrenic nerve conduction studies and needle electrode examination of the diaphragm assess the integrity of phrenic innervation and respiratory muscle function. When neuropathic dysfunction is present, estimating the degree of axon loss and demyelination can help determine prognosis for recovery of respiratory function, and may facilitate consideration of additional interventions such as diaphragmatic pacing.

Visualizing the Diaphragm

Needle electrode placement can be challenging due to the movement of the diaphragm during breathing, as well as its proximity to the lung, pleura, rib periosteum, peritoneum and abdominal viscera. The exam is further complicated when the patient is obese, the diaphragm is atrophic or the diaphragm is in an atypical position due to complete diaphragm paralysis or lung hyperinflation (e.g., in a patient with prior severe obstructive pulmonary disease).

Ultrasound is ideal for imaging soft tissues in real time and guiding the needle electrode to its intended target. The diaphragm can be visualized between the lower ribs in the anterior axillary line, deep to the subcutaneous tissue and intercostal muscles. A normal diaphragm
thickens due to muscle contraction during inspiration and, thus, the quality and degree of diaphragm movement can be observed. A needle electrode insertion site below the pleural space and lung is selected, and the needle can be advanced under direct visualization into the diaphragm muscle. In our experience in the electromyography laboratory at Cleveland Clinic, the result is a safer, more accurate procedure, yielding valuable clinical information.

Steven Shook, MD, is a neurologist with Cleveland Clinic’s Neuromuscular Center. His specialty interests include neuromuscular medicine, electromyography, peripheral nerve injury, entrapment neuropathies, nerve tumors, ultrasound of peripheral nerve and muscle, and MR neurography. He can be contacted at 216.444.7450 or shooks@ccf.org.

SUGGESTED READING


Focal Cerebral Arteriopathy of Childhood

By Neil Friedman, MBChB

Arteriopathies, as a group, constitute an important part of pediatric arterial ischemic stroke (AIS). In a recently published paper from the International Pediatric Stroke Study (IPSS) consortium, 53 percent of children with AIS who underwent vascular imaging studies had an identified arteriopathy.1 The presence of an arterial abnormality does not, however, imply an understanding of the underlying mechanism/pathophysiology or etiology.

Vascular abnormalities are a significant risk for recurrent AIS, and this risk appears to be highest in the first six months after initial stroke presentation.2,3 A population-based cohort study in California showed a five-year cumulative recurrence stroke risk rate of 66 percent in those children with abnormal vascular imaging studies vs. no recurrences among children with normal vascular imaging studies.4

While some arteriopathies (dissection, moyamoya, vasculitis) are well defined, the etiology of one of the largest groups of arteriopathies, the so-called “transient cerebral arteriopathy,” remains uncertain.

**Post-Varicella Arteriopathy**

Transient cerebral arteriopathy (TCA)3 is the terminology that was coined initially to describe a unilateral, focal stenosis of the distal internal carotid artery or proximal middle or anterior cerebral artery, with resultant lenticulostriate infarct. The presentation appears to be “stereotypic” and the result of a monophasic event, although angiographic data have shown that the stenosis may worsen over a three- to six-month period, with persistent focal narrowing of the vessel in a significant number of cases.

The term TCA has been used interchangeably with focal arterial stenosis in childhood (FAC), and the IPSS consortium recently proposed the term “focal cerebral arteriopathy of childhood” (FCA). The pathophysiology is still not fully understood, but a post-infectious inflammatory mechanism has been proposed, given the strong association between FCA and a preceding varicella infection (post-varicella arteriopathy) and similar angiographic appearance that has been associated with other infectious agents.

**Tools for Imaging Vessels**

Understanding the pathophysiology and determining the mechanism for stroke in FCA is a major focus of research in pediatric stroke, given the frequency (20 to 30 percent of all identified arteriopathies)2,3 and recurrence risk (up to 18 percent in some series).5 Insights may come in the near future from an anticipated National Institutes of Health-funded clinical trial in pediatric stroke.

Whether steroids/immunosuppressive agents, with or without antiviral medication, impact outcome and recurrence of stroke in FCA is not known. Similarly, it is unclear whether adjunctive antiplatelet or anticoagulation therapy during the acute phase or the long term is necessary. Attempts to classify the etiology — specifically, vascular abnormalities in childhood AIS — are therefore important to enable correct treatment and establish potential recurrence risk.

Magnetic resonance angiography (MRA) is a readily available and sensitive tool for assessing the intracranial and extracranial vessels. The sensitivity of MRA in detecting extracranial dissection can be increased by obtaining fat-saturated views. MRA is not very sensitive for small-vessel disease, and may overestimate the degree of stenosis.6 Studies have shown, however, that MRA in pediatric AIS may be as sensitive as formal four-vessel cerebral angiography (CA) for large-vessel disease.6

MRA requires sedation in younger children unable to lie still for a prolonged period of time. This problem can be overcome by using CT angiography (CTA); however, CTA requires a large-bore intravenous access for rapid administration of contrast, and exposes the child to relatively high levels of irradiation and potentially adverse reaction to the iodide contrast.
At Cleveland Clinic, CA remains the gold standard for imaging vessels — especially if diagnosis remains uncertain, the MRA is “equivocal” or small-vessel disease such as vasculitis is a concern. Most significantly, we find that comprehensive imaging in a dedicated pediatric stroke center has substantially improved the diagnostic yield with respect to etiology in pediatric stroke, supporting findings from other groups working in this field.

Neil Friedman, MBChB, is a pediatric neurologist specializing in pediatric stroke, pediatric neuromuscular disease, fetal neurology and the neurological complications of pediatric congenital heart disease. He can be contacted at 216.444.6772 or friedmn@ccf.org.

REFERENCES


Functional Magnetic Stimulation for the Treatment of Respiratory Dysfunction in Patients with Spinal Cord Injury

By Vernon W.H. Lin, MD, PhD

Respiratory dysfunction is a major cause of mortality and morbidity in patients with spinal cord injury. Functional magnetic stimulation (FMS) is an emerging technology that has shown clinical efficacy in inspiratory/expiratory muscle training, ventilatory assistance and cough production in these patients.

The magnetic stimulator activates nerves and muscles to produce needed bodily functions such as respiration. The electromagnetic field generated from the round magnetic coil passes easily through highly resistant structures such as skin, fat and bone. FMS can be applied as a noninvasive tool to activate the inspiratory and expiratory muscles by placing coils at different places along an individual’s back.

Useful in High Cervical Tetraplegia and Paraplegia

We have found that magnetic stimulation of the cervical and upper thoracic nerves produces significant inspiratory volume and pressure, of particular benefit to patients with high cervical tetraplegia, who often suffer inspiratory and expiratory muscle dysfunction.

Often, patients with tetraplegia and paraplegia have expiratory muscle dysfunction and impaired cough. FMS of the lower thoracic nerves produces sufficient expiratory volume, pressure and flow to simulate an effective cough, and may potentially condition patients’ expiratory muscles and improve their ability to cough.

In a study by Lin et al. in the Archives of Physical Medicine & Rehabilitation (1998), we reported that training expiratory muscles for four weeks using FMS resulted in significant improvement over baseline in voluntary maximal expired pressure (116 percent), volume (173 percent) and flow rate (123 percent).

Noninvasive and Relatively Pain Free

Compared with functional electrical stimulation (FES), FMS offers many advantages for patients with spinal cord injuries. FMS does not require surgery or electrode implants, thus preventing complications such as infection, bleeding, wire breakage or implant failures. FMS is also less painful and better tolerated than FES.

Unlike needle electrode stimulation, FMS is free of any traumatic risks due to absence of contact with the stimulated structure. No side effects of magnetic stimulation have been reported. FMS can be applied over clothing because it does not require skin contact or electrode gel. Risk of thermal injury from a heated magnetic coil in prolonged stimulation can be prevented by using a thermister-controlled FMS unit and an effective magnetic coil cooling system.

Contraindications to FMS include metal implants in the abdomen or spine, which are subject to mechanical forces exerted by the induced currents. Cardiac pacemakers are a possible contraindication because a magnetic stimulator placed directly over the device could induce sufficient current and voltage to damage its internal electronics.

Modifying the Coil, Aiming for Portability

The FMS laboratory at Cleveland Clinic is collaborating with the Louis Stokes Cleveland VA Medical Center’s FMS Laboratory on a clinical efficacy trial of a modified coil designed by our engineers: the “race track” coil. The new coil’s efficacy in producing inspiratory and expiratory muscle conditioning over six weeks will be compared with a standard respiratory muscle-conditioning protocol.

Both laboratories continue to advance the science and technology associated with FMS for patients with spinal cord injuries. In addition to stimulating respiratory muscles, FMS has demonstrated efficacy when used to enhance gastric emptying, colonic transit, bladder function and, potentially, to prevent deep venous thrombosis. Protocols are being developed to apply these technologies in patients with other neurological diseases and pathologies as well.
Compared with functional electrical stimulation (FES), functional magnetic stimulation (FMS) offers many advantages for patients with spinal cord injuries. FMS does not require surgery or electrode implants, thus preventing complications such as infection, bleeding, wire breakage or implant failures. FMS is also less painful and better tolerated than FES.

Cleveland Clinic’s FMS Laboratory is working on improving the magnetic stimulator’s design and power supply so that a small, portable FMS unit can eventually be manufactured and marketed. The FMS power supply unit’s lack of portability and its bulk are major drawbacks to the use of this very effective clinical tool in patients’ homes and various clinical settings.

Vernon W.H. Lin, MD, PhD, is a neuroscience researcher and Chairman of Cleveland Clinic’s Department of Physical Medicine and Rehabilitation. He and his team have worked on FMS for the past 20 years. Dr. Lin is board certified in physical medicine and rehabilitation as well as spinal cord injury medicine. He can be reached at 216.445.7350 or linv@ccf.org.

SUGGESTED READING


Post-Traumatic Stress Disorder and Athletic Performance

By Joseph W. Janesz, PhD, LICDC, CRC, PCC-S

Performance problems of professional athletes are often associated with undetected psychological injuries such as post-traumatic stress disorder (PTSD). This disorder historically has been underrecognized by professional sports clinicians. Developing a comprehensive and individualized treatment plan to address PTSD is critical because severe physical, psychological and social impairment can result when the disorder is left untreated.

PTSD and Its Effects

Approximately 5 percent of men in the United States will experience PTSD at some point in their lives. PTSD is, in essence, a delayed reaction to trauma, which is defined as an event in a person's past that deeply and profoundly affects the psyche. The person (for purposes of this discussion, a male professional athlete) may begin to view the world as dangerous or life threatening, and believe that he is not equipped to cope effectively with life. A trauma survivor may develop irrational cognitive beliefs that generate high levels of arousal and cause fear, dread, panic, or a profound need to avoid thinking or talking about the traumatic event. The affected person may feel shame and guilt, believing he lacks the strength to overcome his problem.

Many highly successful college football players enter professional sports, but their performance, both on and off the field, never measures up to their promise due to the effects of early childhood trauma. Unaware that PTSD is diminishing player performance, their coaches may presume that such players are unable to make the transition from college to professional ball or that they are not “coachable.”

Resistance to Counseling

The effects of early childhood trauma, combined with the intense demands of professional sports, often cause players to complain of stress, excessive anxiety and worry, especially when a medical injury renders them unable to compete. Yet, these athletes seldom initiate sports counseling. Instead, they may medicate their anxiety and fears by resorting to immature or destructive coping mechanisms, such as drug or alcohol use or sexual impulsivity.

Psychological evaluation may be mandated when a professional athlete violates league conduct policies against substance abuse, driving while intoxicated or domestic violence. The player may resist or only superficially comply with these referrals. As a result, his behavior and athletic performance may become more unpredictable, and his coach may begin to doubt the player's ability to change or to work through his psychological challenges. Without a timely turnaround, the player suffers a potentially career-ending “credibility injury.”

An athlete’s refusal to discuss physical and psychological abuse or severe neglect during childhood is consistent with avoidant cognitive styles associated with PTSD. In addition, he may have limited insight into why a recent injury caused him high levels of anxiety and diminished performance. The player may be unable to work through a life-threatening experience (from a collision on the field) without professional consultation. Formulating a comprehensive, individualized treatment plan to address player problems and psychiatric disorders is paramount.

Diagnosis and Treatment

Obtaining a trauma history and screening for PTSD will assist in determining whether a player is suffering from the disorder. If initial screening suggests PTSD symptoms, a more exhaustive assessment is warranted. A diagnostic interview should be conducted to evaluate each of the 17 PTSD symptoms as outlined in the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition.1

Evidence-based counseling combined with pharmacologic treatment appears to be the most efficacious approach to treating PTSD. Selective serotonin reuptake inhibitors are the medications of choice because they effectively reduce all PTSD symptoms (re-experiencing, avoidance/numbing and hyperarousal).2
In counseling, motivational interviewing promotes therapeutic engagement, and cognitive behavioral therapy is the preferred treatment for trauma disorders.\textsuperscript{3} Judicious use of psychoeducation\textsuperscript{4} and delivery of timely and appropriate levels of care for the player and family are crucial. Development of trust, the therapeutic alliance and prevention of treatment dropout are critical to successful outcomes.\textsuperscript{5}

Joseph W. Janesz, PhD, LICDC, CRC, PCC-S, is a psychotherapist in the Department of Psychiatry and Psychology at Cleveland Clinic. His specialty interests include chemical dependency, executive coaching, organizational development consulting, couples and group therapy, sports counseling and psychotherapy. He can be contacted at 216.444.2199 or janeszj@ccf.org.

REFERENCES


Professional Sports Counseling Model

In 1982, Cleveland Clinic and the Cleveland Browns collaborated to develop and introduce The Inner Circle Program, the first comprehensive professional sports psychiatry and counseling treatment program. Its primary objective is to enhance player performance and quality of life.

This program subsequently became the prototype for the National Football League’s Program for Substances of Abuse and the Player Assistance Program. It remains the model for designing professional sports counseling programs. Cleveland Clinic’s Alcohol and Drug Recovery Center adapted The Inner Circle model as its primary clinical approach for treatment of corporate executives and medical professionals.

Before the program’s initiation among the Browns, immense resources had been invested in enhancing athletic performance by treating physical injuries, employing innovative strength training methods and applying nutritional advances, but the psychiatric and psychosocial needs of the athlete had seldom been identified or treated. Focus of The Inner Circle is on treating the “whole” player: considering his personal goals and aspirations, addressing his psychiatric or behavioral health problems, and dealing with his psychosocial stressors and medical concerns (such as chronic pain or medication management).

The Inner Circle Program promotes a well-coordinated and confidential treatment effort for players by involving management, coaches, trainers, team physicians, sports counselors, psychiatrists, family and others. The approach creates a climate that encourages athletes to seek professional assistance, utilizes motivational interventions to diminish player reluctance or resistance, and leverages the notion that attending to mental health needs enhances athletic performance.

SUGGESTED READING

Systematic Data Collection Enhances Care for Patients with Sleep Apnea

By Charles Bae, MD

Improving quality of life is an important outcome measure for patients with obstructive sleep apnea syndrome (OSAS) who are treated with continuous positive airway pressure (CPAP). However, assessing changes in quality of life accurately and reliably has been challenging. The ability to measure treatment efficacy in an objective manner has been facilitated by the Knowledge Program©.

Within Cleveland Clinic’s Neurological Institute, the Knowledge Program© utilizes the latest interactive technology to overcome barriers to systematic, consistent evaluation of treatment effect on quality of life, depression and other outcomes. A comprehensive database is populated with a wealth of information from disease-specific patient questionnaires and clinical assessments from providers at the point of service.

All patients seen by a provider in the Neurological Institute are asked to complete two questionnaires: the European Quality of Life Questionnaire (EuroQol) to measure health-related quality of life and the Patient Health Questionnaire (PHQ-9), which screens for depression. In addition, each disease-specific center has a set of unique questions that patients and providers may answer. A key aspect of the Knowledge Program is the seamless integration of this data in the patient’s electronic medical record.

The Knowledge Program will help clinical researchers identify patient cohorts to perform both retrospective and prospective analyses to improve patient care and, ultimately, outcomes. Because data from disease-specific centers are aggregated into a central database, collaboration among various subspecialties is inevitable.

Responses Guide Office Visit

Since January 2008, every patient seen in Cleveland Clinic’s Sleep Disorders Center has been asked to complete an electronic questionnaire at every office visit. In the waiting room, patients record their answers on a wireless tablet with a stylus. Questionnaire responses are combined with demographic information, test results and encounter diagnoses to create a discrete patient profile.

In addition to the EuroQol and PHQ-9, patients seen at the Sleep Disorders Center complete an Epworth Sleepiness Scale (ESS), which assesses the likelihood of dozing off in a sedentary situation, and the Fatigue Severity Scale (FSS), which rates the effect of fatigue on various daily activities. Depression that is undiagnosed or unrecognized may mask improvements realized with compliant use of CPAP for some patients with sleep apnea. These different questionnaires allow the provider to tease out the degree to which patient symptoms are due to sleepiness, fatigue or depression.

Among patients with OSAS who used CPAP compliantly (at least four hours a night, six nights a week), levels of daytime sleepiness and fatigue (measured by the ESS and the FSS, respectively) decreased in 2008. Depressive symptoms improved as well, as measured by the PHQ-9 (Figure 1). Many sleep apnea patients using CPAP and experiencing depression, according to the PHQ-9, registered decreases in their scores into the minimally depressed or normal range. Significant overlap exists between depressive symptoms and the effects of chronic partial sleep deprivation that may be caused by OSAS.

Diverse Applications for Data

In the traditional care model of the provider querying the patient during the office visit, many factors (e.g., how the patient perceives the provider, whether the patient understands the question) can affect response, or even introduce bias. Having the patient complete these questionnaires alone, before being seen by the provider, helps reduce potential biases that may obscure areas for improvement.
Since January 2008, every patient seen in Cleveland Clinic’s Sleep Disorders Center has been asked to complete an electronic questionnaire at every office visit. For patients with OSAS, the questionnaires have been useful in documenting the response to CPAP and showing the extent of improvement.

Beyond their value in the immediate office visit, the validated questionnaires that Sleep Disorders Center patients complete can be used to track outcomes individually and in groups over time. For patients with OSAS, the questionnaires have been useful in documenting the response to CPAP and showing the extent of improvement. Providers can easily compare patient responses from previous visits to demonstrate improvements (or decrements) in symptom severity and quality of life.

The Knowledge Program also increases patient participation and involvement in care. The questionnaires can provide an impartial framework for the office visit and help identify areas that need to be addressed regarding patient response to treatment.

Charles Bae, MD, is a sleep disorders specialist in the Sleep Disorders Center at Cleveland Clinic. His specialty interests include sleep apnea, narcolepsy, restless legs syndrome, parasomnias and circadian rhythm disorders. He can be contacted at 216.444.3323 or baec@ccf.org.

Average Change in Sleepiness, Fatigue and Depressive Symptoms before and after Treatment
(N = 212)

* Fatigue Severity Scale
(Standard deviation 5.6 pretreatment, 4.9 post-treatment)

** Epworth Sleepiness Scale
(Standard deviation 14.2 pretreatment, 15.3 post-treatment)

*** Patient Health Questionnaire
(Standard deviation 6.4 pretreatment, 5.6 post-treatment)

Figure 1: Fatigue, sleepiness and depressive symptoms decreased among sleep apnea patients who received continuous positive airway pressure (CPAP) treatment.

By Michael Steinmetz, MD

An innovative immune system modulation therapy appears promising for treatment of secondary spinal cord damage following trauma. In our laboratory animal model, a combination therapy resulted in significant functional improvement within weeks of spinal cord injury.

Currently, there is no effective therapy for acute spinal cord injury. Options include surgical decompression and/or intravenous methylprednisolone. Despite promise in animal models, the clinical effectiveness of i.v. methylprednisolone remains controversial.

Much is known about the ongoing damage that occurs to the spinal cord following injury — a process termed secondary injury — but an effective clinical strategy is still lacking. Significant research on therapeutic strategies has sought to limit or attenuate this injury cascade. Our research strategy has aimed to limit this injury cascade at multiple points, in the hope of improved tissue sparing and overall functional recovery.

A Multi-Factorial Challenge

The immune response initiated by the primary spinal cord injury is central to the cascade of events leading to secondary damage. Infiltration of the spinal cord by neutrophils, macrophages and monocytes commences within hours and continues for days and weeks after the initial injury. These cells release substances that directly damage the spinal cord, and also recruit or stimulate other cells to induce further damage. Ultimately, a glial scar forms; this scar or region around it contains molecules inhibitory to regrowth of the injured neurons. Interestingly, substances released from macrophages have also been found to promote or stimulate the regeneration of injured axons. This dichotomy remains poorly understood.

The primary acute spinal cord injury and immediate damage are uncontrollable. They could be altered only by initiatives such as public awareness campaigns and/or laws; for example, mandatory seat belt usage. The treatment goal for patients with spinal cord injury, therefore, is to limit the secondary damage by preserving neurons and other critical cells and promoting axonal regrowth. This is a multi-factorial challenge, in that the growth-inhibitory molecules that actively block neuronal regeneration must be mitigated at the same time regeneration is stimulated.

In collaboration with Jerry Silver, PhD, of Case Western Reserve University, who is responsible for some of the foundational work on macrophages and spinal cord injury and regeneration, our research focuses on the role of macrophages in secondary injury.

Research by Dr. Silver and colleagues has demonstrated that macrophages exert an effect on damaged spinal cord neurons that results in their “die-back,” which suggests that controlling macrophage presence or function could enhance tissue sparing after injury and axonal regrowth. In our laboratory, we are using a combinatorial approach with inflammatory response modulators to limit the number of macrophages that infiltrate the injury site and to increase both the survival and intrinsic growth of the spinal cord axons.

Early Results Point to Preservation

The substances we are testing in the animal model are approved for human use for other indications. This fact is highly significant in that if these treatments prove to be effective, they may be rapidly translated to clinical human trials. Treatment is initiated immediately subsequent to the contusion injury, with one drug administered in a series of four intraperitoneal injections and the second drug given continuously by subcutaneous pump for 14 days.

After one month of treatment, laboratory rats demonstrated much greater increases in hind limb walking ability compared with control animals. The treated animals have also demonstrated recovery of certain waveforms that may be measured using physiologic techniques (somatosensory evoked potential recording). These improvements are suggestive of neuronal and/or oligodendrocyte preservation. Indeed, analysis of spinal cord tissue demonstrates significant axon and myelin sparing in treated vs. control rats. The degree and extent of the spinal cord damage are much smaller in treated animals. Axonal tracing studies have demonstrated significant increases in the degree of axonal sparing and regeneration in the animals that showed functional recovery.
In the next investigative phase, we plan to refine the project in several ways. Our interests include altering the timing of the intervention, studying the electrophysiology of the functional improvement, and evaluating bladder function recovery and characterization. Spinal cord injury patients rank recovery of bladder function high on their list of desired outcomes.

An additional avenue that bears investigation is the use of combinatorial medical treatment in conjunction with stem cell therapy. Embryonic stem cells have demonstrated ability to remyelinate surviving axons and bridge the injury site. The Food and Drug Administration recently approved a Phase I clinical trial to study the safety of an embryonic stem cells line in patients who have suffered an acute spinal cord injury. Our hope is that our pharmacologic strategy may be combined with stem cell transplantation, with the aim of promoting significant spinal cord protection and further recovery and remyelination of surviving axons following injury. Evaluation of this approach is among our long-term research goals.

Michael Steinmetz, MD, is a neurological surgeon in the Center for Spine Health at Cleveland Clinic. His specialty interests include spine deformity, adult scoliosis, adult kyphosis, reconstructive spine surgery and spinal cord injury. He can be contacted at 216.445.4633 or steinmm@ccf.org.

Cleveland Clinic Spine Research

The scope of spine research in the Neurological Institute includes the work of the Spine Research Laboratory (SRL) under the direction of Lars Gilbertson, PhD. The SRL is dedicated to improving the quality of life for people with spinal disorders through research, innovation and education. Recently relocated to new facilities at Lutheran Hospital, a Cleveland Clinic hospital, the laboratory includes a state-of-the-art spine biomechanics laboratory, a computational simulation laboratory and a tissue engineering facility.

With the goal of translating the most promising bench results into clinical applications, the Spine Research Laboratory is focused on innovative strategies for improving spinal instrumentation; new technologies for in vivo monitoring and measurement of biomechanical and physiological properties of the intervertebral disc; and development of artificial disc technologies to preserve spinal motion. A robotics-based mechanical testing facility and a prototype fabrication laboratory are the sites of ongoing research into spine biomechanics, surgical spinal stabilization technology and spinal micro-electro-mechanical systems (MEMS) — a collaborative effort led by Edward Benzel, MD, with Aaron Fleischman, PhD, of Cleveland Clinic Lerner Research Institute.

The Spine Research Laboratory is the recipient of a five-year Third Frontier Commission grant from the State of Ohio for spinal implant development, in collaboration with the University of Toledo and the Clinical Tissue Engineering Center.

Control (left column) and treated spinal cords five weeks after injury.

A and B: NF-H stains neurons. Spinal cords treated with two inflammatory response modulators show a larger number of axons (arrows) in tissue surrounding the injury site following the combined treatment.

C and D: MBP stains myelin. A greater number of myelin profiles (arrows) and less myelin debris (dots) were observed after the combined treatment, signifying greater myelin sparing.

E and F: NF/MBP double-labeling reveals a larger number of myelinated axons (arrowheads), fewer demyelinated axons (arrows) and less myelin debris (dots) after treatment, again signifying greater tissue sparing and likely functional sparing, in that spared axons are surrounded by myelin.
Continuing Medical Education

All physicians are cordially invited to attend the following Cleveland Clinic Neurological Institute CME symposia and ongoing programs.

**SEPTEMBER 4, 2009**
**Acute Stroke Update**
Course Directors: Peter Rasmussen, MD, and Irene Katzan, MD
*InterContinental Hotel & Bank of America Conference Center, Cleveland, Ohio*

**SEPTEMBER 11-12, 2009**
**Neuro-Oncology Symposium**
Course Directors: Gene Barnett, MD, and David Peereboom, MD
*Ritz-Carlton Cleveland, Ohio*

**SEPTEMBER 25, 2009**
**7th Annual Pediatric Neurology Update**
Course Directors: Manikum Moodley, MD, and Neil Friedman, MBChB
*Executive Caterers at Landerhaven Mayfield Heights, Ohio*

**OCTOBER 3, 2009**
**Spasticity Management in Motion Symposium**
Course Directors: Francois Bethoux, MD, and Mark Luciano, MD, PhD
*Bertram Inn & Conference Center Aurora, Ohio*

**OCTOBER 9, 2009**
**The Anger Solution**
Course Director: Joseph Janesz, PhD
*Embassy Suites Cleveland – Rockside Independence, Ohio*

**OCTOBER 27-28, 2009**
**The Leon Thal Symposium for the Prevention of Dementia 2009**
Course Directors: Zaven Khachaturian, PhD, and Ara Khachaturian, PhD
*Wynn Hotel Las Vegas, Nevada*

**OCTOBER 29, 2009**
**4th Annual PTSD Symposium**
Course Director: Joseph Janesz, PhD
*InterContinental Hotel & Bank of America Conference Center, Cleveland, Ohio*

**OCTOBER 29-30, 2009**
**Clinical Trials in Alzheimer’s Disease**
Course Directors: Zaven Khachaturian, PhD; Jacques Touchon, MD; and Bruno Vellas, MD
*Wynn Hotel Las Vegas, Nevada*

**NOVEMBER 7, 2009**
**Spine Care for the Primary Care Physician**
Course Directors: Gordon Bell, MD, and Daniel Mazanec, MD
*Lerner Research Institute – Amphitheater Cleveland Clinic Main Campus Cleveland, Ohio*

**DECEMBER 7-11, 2009**
**Leksell Gamma Knife Perexion Course**
Course Directors: Gene Barnett, MD, and John Suh, MD
*Gamma Knife Center Cleveland Clinic Main Campus Cleveland, Ohio*

**FEBRUARY 15-19, 2010**
**Leksell Gamma Knife Perexion Course**
Course Directors: Gene Barnett, MD, and John Suh, MD
*Gamma Knife Center Cleveland Clinic Main Campus Cleveland, Ohio*

For more information, please visit clevelandclinic.org/neuroscience/CME
Neurological Institute  Select Clinical Trials

The Neurological Institute prioritizes its offer of new research developments and clinical therapeutic trials to patients with neurological problems. We have more than 140 clinical research trials currently under way, with supported funding of more than $17 million. For more information on all of our clinical trials, please call our Neurological Institute Research and Development office at 216.444.3507 or visit clevelandclinic.org/neurotrials.

**BRAIN HEALTH**

Cognitive and Functional Brain Changes in Preclinical Huntington's Disease
The purpose of this five-year project is to use fMRI to gain a comprehensive understanding of the pattern and natural history of brain dysfunction in preclinical HD.

**Principal Investigator:** Stephen Rao, PhD  
**Contact:** Christine Reece, 216.445.9833

Neural and Behavioral Sequelae of Blast-Related Traumatic Brain Injury
The primary goal of this study is to use advanced imaging tools (fMRI, DTI) to understand the impact of blast TBI on the brain.

**Principal Investigator:** Stephen Rao, PhD  
**Contact:** Christine Reece, 216.445.9833

Goldman Algorithm: For the Treatment of Depression Associated with Multiple Sclerosis
The purpose of this study is to determine the feasibility of the algorithm (the Goldman Algorithm), which provides an evidence-based, step-wise approach to the assessment and treatment of depressive syndromes as they occur among persons with MS.

**Principal Investigator:** Randolph Schiffer, MD  
**Contact:** Christine Reece, 216.445.9833

**BRAIN TUMOR**

Phase II Trial of Sunitinib as Maintenance Therapy after Stereotactic Radiosurgery in Patients with 1-3 Newly Diagnosed Brain Metastases
The purpose of this trial is to determine the CNS progression-free survival rate in patients with 1-3 brain metastases who receive stereotactic radiosurgery followed by sunitinib.

**Principal Investigator:** David Peereboom, MD  
**Contact:** Cathy Brewer, RN, 216.444.7937

Clinical Study to Assess Entry of Chemotherapeutic Agents into Brain Metastases in Women with Breast Cancer
The purpose of this trial is to determine the concentration of certain chemotherapeutic drugs in brain metastases from breast cancer.

**Principal Investigator:** Robert Weil, MD  
**Contact:** Cathy Brewer, RN, 216.444.7937

**CEREBROVASCULAR**

Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAAMPRIS)
SAAMPRIS seeks to determine whether stenting plus aggressive medical management vs. aggressive medical management alone prevents ischemic stroke up to two years. In this study, patients will be randomized to one of the two treatment arms. Modifiable risk factors will be assessed in all patients. Aggressive medical management with study oversight and management will include hypertension and hyperlipidemia. A lifestyle coach will be provided to each enrolled participant. The study staff will communicate with the primary care physician for smoking cessation, diabetes control and other modifiable risk factors. Anti-platelet, anti-hypertensive and cholesterol/lipid-lowering medications may be provided to the patient.

**Principal Investigator:** Irene Katzan, MD, MS  
**Contact:** Doreen Andrews-Hinders, BS, RN, CCRP, 216.445.9243

**TIAMI 50**
TIAMI is a placebo-controlled trial of an investigational new anti-platelet drug therapy to evaluate whether there is a reduction of ischemic events in patients with a history of symptomatic athrosclerosis of the coronary, cerebral or peripheral vascular system. Patients who are eligible to enroll in this study may continue on standard-of-care anti-platelet therapy and will be randomized to placebo or the investigational drug (SCH 530348). The mechanism of action for this new drug is inhibition of thrombin on platelets. When added to current anti-platelet regimen, it is hypothesized that there will be a reduction of ischemic vascular events.

**Principal Investigator:** Irene Katzan, MD, MS  
**Contact:** Carissa Kirkka, RN, 216.636.0302

**EPILEPSY**

Prospective Randomized 12-Week Controlled Study of Visual Field Change in Subjects with Partial Seizures Receiving Pregabalin or Placebo
The purpose of the study is to monitor visual fields in subjects with partial epilepsy receiving pregabalin or placebo for 12 weeks, under highly controlled conditions.

**Principal Investigator:** Dileep Nair, MD  
**Contact:** Cindy Rose, 216.444.9874

Overcoming Genetic Heterogeneity in the Epilepsies
The objective of this mentored, patient-oriented research career development award is to use novel methods of linkage analysis and epilepsy phenotyping to overcome genetic heterogeneity in gene-mapping efforts.

**Principal Investigator:** Jocelyn Bautista, MD  
**Contact:** Cindy Rose, 216.444.9874

Responsive Neurostimulator (RNS™) System Pivotal Clinical Investigation
The purpose of this study is to assess the safety of the RNS system and to demonstrate its effectiveness as an adjunctive therapy in reducing the frequency of seizures in individuals age 18 years of age or older with partial onset seizures that are refractory to two or more anti-epileptic medications.

**Principal Investigator:** Dileep Nair, MD  
**Contact:** Veronica Spriggs, 216.444.9961
Neurological Institute Select Clinical Trials

Tools for Large-Scale Platform-Independent MEG Data Analysis

The purpose of this study is to develop a standard work flow for the analysis of MEG and EEG data, coupled with specification of data structures to enable cross-site data sharing and comparison of results. The study will begin to define standard analysis procedures for MEG, with associated calibration and testing metrics to ensure fidelity of the data and results.

Principal Investigator: John Mosher, PhD
Contact: Jocelyn Riley, BS, CCRP, 216.444.8638

HEADACHE

fMRI of the Brain Stem in Migraine Sufferers and Controls

The purpose of this trial is to determine if iron deposition correlates with progression of disease. In this trial, non-headache subjects as well as those with episodic migraine and chronic daily headache will receive an fMRI to evaluate markers for disease progression in migraine vs. non-headache brain.

Principal Investigator: Stewart J. Tepper, MD
Contact: Mary R. Horvat, BA, CCRP, 216.445.1947

A Multicenter, Randomized, Double-Blind, Placebo- and Active-Controlled Crossover Study to Evaluate the Safety and Efficacy of MK-0974 in the Treatment of Acute Migraine in Patients with Stable Vascular Disease

In this trial, patients with episodic migraine will enroll in a large, multicenter, placebo-controlled Phase II trial of gabapentin enacarbil, a produg of gabapentin with dramatically improved pharmacokinetics, in migraine prevention.

Principal Investigator: Stewart J. Tepper, MD
Contact: Mary R. Horvat, BA, CCRP, 216.445.1947

MULTIPLE SCLEROSIS

A Randomized, Multicenter, Placebo-Controlled and Active Reference (Glatiramer Acetate) Comparison Study to Evaluate the Efficacy and Safety of BG00012 in Subjects with Relapsing-Remitting Multiple Sclerosis

The purpose of this study is to assess the efficacy, safety and tolerability of oral BG00012 in a two-year, double-blind, placebo-controlled trial. Outcome measures include clinical relapses and progressive disability. In addition, a comparative benefit/risk assessment will be made between BG00012 and glatiramer acetate (Copaxone®).

Principal Investigator: Robert J. Fox, MD
Contact: Cynthia Schwanger, RN, MScN, 216.445.5788

A Dose-Ranging Study Evaluating the Efficacy, Safety and Tolerability of GSK1838262 (XP13512) in the Prophylactic Treatment of Migraine Headache

In this trial, patients with episodic migraine will enroll in a large, multicenter, placebo-controlled Phase II trial of gabapentin enacarbil, a produg of gabapentin with dramatically improved pharmacokinetics, in migraine prevention.

Principal Investigator: Stewart J. Tepper, MD
Contact: Mary R. Horvat, BA, CCRP, 216.445.1947

MULTIPLE SCLEROSIS

A Double-Blind, Randomized, Multicenter, Placebo-Controlled, Parallel-Group Study Comparing the Efficacy and Safety of 1.25 mg FTY720 Administered Orally Once Daily vs. Placebo in Patients with Primary Progressive Multiple Sclerosis (PPMS)

The purpose of this study is to evaluate whether FTY720 is effective in delaying MS disability progression in the absence of relapses compared with placebo. The present study is a double-blind, placebo-controlled study to evaluate the efficacy and safety of FTY720 1.25 mg compared with placebo in patients with PPMS.

Principal Investigator: Alexander Rae-Grant, MD
Contact: Cynthia Schwanger, RN, MScN, 216.445.5788

RECLAIM Deep Brain Stimulation (DBS) Clinical Study for Treatment-Resistant Depression

The purpose of this study is to evaluate the safety and efficacy of bilateral DBS of the ventral capsule/ventral striatum (VC/VS) as an adjunctive therapy for treatment-resistant depression.

Principal Investigator: Donald Malone Jr., MD
Contact: Jenna Stump, CCRP, 216.444.2673, or Patty St. Marie, RN, CCRP, 216.445.3125

A Multicenter, Phase III Study Comparing Two Doses of Alemtuzumab (CAMPATH-1h) with Rebif® in Patients with Relapsing-Remitting Multiple Sclerosis

The purpose of this study is to compare the effect of alemtuzumab with Rebif on MS-related disability and relapses as well as harmful effects on the brain that patients with MS may experience. This study also seeks to examine any side effects patients may experience when taking alemtuzumab or Rebif. This study is sponsored by Genzyme Corporation.

Principal Investigator: Jeffrey Cohen, MD
Contact: Vinette Zinkand, RN, CCRP, 216.444.4817

Controlled Trial of Deep Brain Stimulation for Obsessive-Compulsive Disorder (OCD)

The purpose of this study is to determine the effects of three months of masked VCVS stimulation on OCD symptoms, functioning and quality of life compared with sham stimulation in patients with treatment-resistant OCD.

Principal Investigator: Donald Malone Jr., MD
Contact: Jenna Stump, CCRP, 216.444.2673, or Patty St. Marie, RN, CCRP, 216.445.3125
A Pilot Study Examining the Extent of Involvement of the Autonomic Nervous System in Complex Regional Pain Syndrome (CRPS II) and its Impact on the Peripheral Nervous System, Heart and Brain

The purpose of this study is to define the link between alpha-adrenergic receptor supersensitivity and the autonomic sympathetic symptoms observed at the level of the affected limb in CRPS I, a systemic disease of the autonomic nervous system. The study seeks to determine the presence or absence of generalized dysautonomia in CRPS I, specifically at the level of the sudomotor system, the cardiovascular system, the pupil and its control centers in the brain.

Principal Investigator: Kamal R. Chémali, MD
Contact: Nicole Berry, CCRP, 216.445.1741

Clinical Trial of Ceftriaxone in Subjects with Amyotrophic Lateral Sclerosis (ALS)

The objectives of this study are to determine the pharmacokinetics and tolerability of long-term ceftriaxone treatment and to subsequently determine the efficacy of this treatment in subjects with ALS. The study will measure multiple aspects of decline in subjects with ALS and correlate these outcome measures with the change in survival due to treatment effect.

Principal Investigator: Rebecca McCarrer-Kuenzler, MD
Contact: Nicole Berry, CCRP, 216.445.1741

Validation of NIH Stroke Scales in Children

The purpose of this project is to evaluate the validity and utility of a pediatric adaptation of the NIHSS (PeNIHSS). The results of this study will provide new information on how initial clinical stroke severity is related to size and location of the stroke; its importance in predicting outcome in children; and the influence of age, gender and stroke risk factor on the prediction of outcome.

Principal Investigator: Neil Friedman, MBchB
Contact: Diane Davies, 216.444.0173

Bipolar Disorder in Pregnancy and the Postpartum Period: Predictors of Morbidity

The purpose of this study is to systematically follow and assess women during pregnancy and six months postpartum to quantify recurrence risk and identify morbidity predictors, with particular emphasis on the adequacy of pharmacotherapy.

Principal Investigator: Adele C. Viguera, MD, MPH
Contact: Judith Meinert, ACSW, LISW, CCRP, 216.445.7168

Citalopram vs. Placebo for the Treatment of Symptomatic Peri- and Postmenopausal Women with Epilepsy: Impact on Depression, Vasomotor Symptoms, Sleep and Quality of Life

The purpose of this study is to examine the efficacy, tolerability and safety of citalopram, a serotonin reuptake inhibitor, compared with placebo in treating depression in peri- and postmenopausal women with epilepsy.

Principal Investigator: Adele C. Viguera, MD, MPH
Contact: Judith Meinert, ACSW, LISW, CCRP, 216.445.7168

SLEEP

Preoperative Polysomnographic Assessment of Cardiac Surgery Inpatients

The purpose of this study is to compare the effectiveness of diagnosing obstructive sleep apnea using a wireless sleep study device called Crystal 20-H with sleep questionnaires commonly used in sleep disorders centers.

Principal Investigator: Nancy Foldvary-Schaefer, DO
Contact: Stella Baccaray, RN, MSN, 216.444.6718

An Assessment of P-15 Bone Putty in Anterior Cervical Fusion with Instrumentation

The purpose of this study is to evaluate whether P-15 bone putty is not inferior in effectiveness and safety to local autologous bone when applied in Level I instrumented anterior cervical discectomy and fusion with the use of a structural allograft ring in patients with degenerative cervical disc disease.

Principal Investigator: Iain Kalfas, MD
Contact: Diane Fabec, RN, CCRP, 216.445.7744

Randomized Controlled Trial of Duragen Plus Adhesion Barrier Matrix to Minimize Adhesions Following Lumbar Discectomy

The purpose of this study is to evaluate the safety and effectiveness of an experimental product (Duragen Plus Adhesion Barrier Matrix) to be used as an adhesion barrier in spinal surgery, which may help minimize postoperative scarring and the pain that may result from that scarring, compared with a control group receiving standard of care (surgery without an adhesion barrier).

Principal Investigator: Edward Benzel, MD
Contact: Diane Fabec, RN, CCRP, 216.445.7744

Cervical Spondylotic Myelopathy (CSM) Study: Anterior vs. Posterior

This study seeks to determine the optimal surgical approach for patients with multilevel CSM. This study is for patients with spinal cord compression (two or more levels) from degenerative cervical spondylotic with clinical myelopathy, who will be treated with either ventral decompression with or without fusion. Excluded from the study are patients with cervical kyphosis greater than five degrees; a segmental kyphotic deformity of three or more disc-octaphyes that extend dorsal to a line drawn from the dorsal caudal point of the C2 to the dorsal caudal point of the C7, ossification of the posterior longitudinal ligament; or developmental spinal canal narrowing (12 mm).

Principal Investigator: Edward Benzel, MD
Contact: Diane Fabec, RN, CCRP, 216.445.7744
Referrals

24/7 hospital transfers or physician consults
800.553.5056

Neurological Institute Contact Center
Centralized scheduling that allows patients to make appointments with any NI physician at any location at 216.636.5860 or toll-free 866.588.2264

Web
clevelandclinic.org/neuroscience

Services for Physicians

Physician Directory View all Cleveland Clinic staff online at clevelandclinic.org/staff.

Physician Liaison Referring physicians have a direct and personal link to Cleveland Clinic with our Physician Liaison. For help with any interaction involving Cleveland Clinic, contact Physician Liaison Kate Kenny at clevelandclinic.org/ContactKate.

Critical Care Transport Worldwide Cleveland Clinic’s critical care transport team serves critically ill and highly complex patients across the globe. The transport fleet comprises mobile ICU vehicles, helicopters and fixed-wing aircraft. The transport teams are staffed by physicians, critical care nurse practitioners, critical care nurses, paramedics and ancillary staff, and are customized to meet the needs of the patient. Critical care transport is available for children and adults.

To arrange a transfer for STEMI (ST elevated myocardial infarction), acute stroke, ICH (intracerebral hemorrhage), SAH (subarachnoid hemorrhage) or aortic syndromes, call 877.279.CODE (2633).

For all other critical care transfers, call 216.444.8302 or 800.553.5056.

Track Your Patient’s Care Online Whether you are referring from near or far, DrConnect offers secure access to your patient’s treatment progress at Cleveland Clinic. To establish a DrConnect account, visit clevelandclinic.org/drconnect or email drconnect@ccf.org.

Outcomes Data Available The latest Outcomes book from the Cleveland Clinic Neurological Institute is available. Our Outcomes books contain clinical outcomes data and information on volumes, innovations, research and publications. To view Outcomes books for many Cleveland Clinic institutes, visit clevelandclinic.org/quality.

CME Opportunities: Live and Online Cleveland Clinic’s Center for Continuing Education’s website, clevelandclinicmeded.com, offers convenient, complimentary learning opportunities, from webcasts and podcasts to a host of medical publications and a schedule of live CME courses. Many live CME courses are hosted in Cleveland, an economical option for business travel. Physicians can manage their CME credits by using the myCME Web Portal, available 24/7.

Services for Patients

Remote Consults Request a remote medical second opinion from Cleveland Clinic. MyConsult is particularly valuable for patients who wish to avoid the time and expense of travel. Visit clevelandclinic.org/myconsult, email eclevelandclinic@ccf.org or call 800.223.2273, ext. 43223.

Medical Concierge Complimentary assistance for out-of-state patients and families 800.223.2273, ext. 55580, or email medicalconcierge@ccf.org.

Global Patient Services Complimentary assistance for national and international patients and families, 001.216.444.8184 or visit clevelandclinic.org/gps.

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Cleveland Clinic DrConnect is a complimentary service providing our referring physician colleagues secure, online access to the electronic medical record information related to a patient’s treatment progress. If you would like to receive your next patient report electronically, please log onto www.clevelandclinic.org/drconnect to establish your own DrConnect account.