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The Spine Care Path: An Evolving Tool to Curb Variation from Best Practice — Daniel Mazanec, MD

How Much Change Is Enough to Matter? Determining Minimal Clinically Important Differences for Health Status Measures — Sandra D. Griffith, PhD; Deborah M. Miller, PhD; and Irene L. Katzan, MD

On the cover: Neurosurgeon Jorge Gonzalez-Martinez, MD, PhD, performs epilepsy surgery similar to the novel technique reported on pages 14-17 combining robot-assisted stereotactic laser ablation with intraoperative MRI.
DEAR COLLEAGUES,

Innovation in healthcare is heralded today as much as it’s ever been, but do we use the term “innovation” as inclusively as we should? We are quick to apply it to new therapies and diagnostic methods, but we are slower to use it to describe changes in processes or systems — even when such changes stand to deliver greater healthcare value at the population level.

Here in Cleveland Clinic’s Neurological Institute, we’ve been focusing a great deal of attention on the value equation in healthcare, and that focus has led to some notable innovations in realms beyond the traditional laboratory or clinical trial setting.

A prime example is the Neurological Institute’s lead role in the Cleveland Clinic Care Path initiative, which has been extended across all of Cleveland Clinic, spawning more than 50 disease-specific care paths that are in development or have been completed. Care paths are more than just practice guidelines; they are electronic tools built on top of guidelines to help providers make guidelines operational. The impetus for our care paths is value-based care delivery, particularly in terms of standardization of care across time, venues and provider types. Our objective is to reduce unnecessary variation from the most evidence-based, patient-centered and efficient standard of care.

Two care paths figure prominently in this issue of Neuroscience Pathways — the Concussion Care Path discussed on page 10 and the Spine Care Path detailed on page 37. These articles provide snapshots of how we are using care paths as the organizing principle to align our services to provide patients with the highest-quality care in the most timely and efficient manner possible. In other words, to deliver value.

Equally central to the value equation is measurement of meaningful outcomes and use of those measurements to drive continuous improvement. The final article in this issue, from our Center for Outcomes Research and Evaluation (page 40), spotlights some inventive work we’re doing to determine which changes in health status measures are truly clinically meaningful and to apply those insights at scale to deliver value for individuals and populations alike.

Along with these articles we’ve included others from across the Neurological Institute that profile more traditional kinds of healthcare innovation, directed at highly specific clinical and research necessities. Those necessities are of course as pressing as they’ve always been. The challenge for us all in today’s landscape is to align our responses to those necessities, whenever possible, to the drive for value in healthcare. The following pages share some examples of our institute’s efforts to do so. I hope you find them edifying, and I invite you to share your thoughts.

Michael T. Modic, MD, FACR
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Mapping biochemical information in the brain has the potential to unlock the biochemical processes involved in neuropsychiatric disorders, which remain poorly understood. Although techniques such as proton magnetic resonance spectroscopy (MRS) have yielded insight into the workings of the brain, these techniques are mostly restricted to single voxels (to obtain relatively large signal over a homogeneous area of brain) and thus to small areas of the brain that sometimes may not be relevant to psychiatric illness. In addition to single-voxel spectroscopy, multivoxel MR spectroscopic imaging (MRSI) has long been used in spectroscopy studies, but MRSI studies often scan over a single slice and require long scan times to obtain useful information.

As imaging tools are refined, knowledge of brain neurochemistry in neuropsychiatric disorders will expand, promising better disease detection, superior therapy monitoring and improved drug development. New imaging methods and techniques to map metabolites in larger volumes of the brain are being developed to accomplish these goals. Advances in hardware and pulse sequences have already made it possible to scan a much larger portion of the brain in three dimensions (3-D) with good signal-to-noise ratio and in reasonable scan time.¹⁻³

This article highlights the advantage of building on these advances by performing 3-D MRSI to gain clinical insights, and it discusses the potential for future insights with the recent arrival of a 7-tesla (7T) MRI scanner at Cleveland Clinic.

Whole Brain 3-D Magnetic Resonance Spectroscopy

MRSI, also known as chemical shift imaging, records spectroscopic data for a group of voxels using an MRI scanner. To date, attempts to characterize the neurobiological basis of psychiatric illness have used proton MRSI to noninvasively measure the neurochemical environment within the brain. The neurochemicals most commonly visualized are:

- Lactate
- The metabolites N-acetylaspartate (NAA), creatine (Cr) and choline (Cho)
- The amino acids γ-aminobutyric acid (GABA), glutamate and glutamine

Abnormalities in concentrations of these metabolites are indicators of abnormal neuronal energy metabolism, which is known to occur in several neuropsychiatric disorders. For technical reasons, a single-voxel design that allows signal detection from a well-defined area and requires shorter measurement times typically has been employed. Unfortunately, measuring localization limits measurement to brain areas that may not be involved in psychiatric illness (e.g., the occipital cortex) and therefore does not provide a meaningful and comprehensive picture of whole brain metabolite concentrations.

Although acquisition times are shorter with single-voxel spectroscopy, that approach is best suited to imaging when a volume of interest is known. Multivoxel spectroscopic methods can present data in 2-D or 3-D images. Multivoxel spectroscopy is able to identify the metabolite profile in brain regions but suffers from long data acquisition times.

Building on Insights from 2-D Studies

In a recent study, Dr. Anand and colleagues,⁴ using a single-slice 2-D technique, reported different concentrations of glutamate in different brain regions among patients with bipolar depression, patients with bipolar mania and healthy controls, whereas concentrations of lactate were uniformly high in all regions.

This discovery has ignited a quest to study chemical changes in large volumes of brain simultaneously. By using 3-D proton echo-planar spectroscopic imaging (PEPSI), brain metabolites can be measured simultaneously from multiple brain regions to accelerate spectra acquisition times. Using a high-spatial-resolution 3-D PEPSI pulse sequence at 3T field strength, high-quality spectra of the metabolites from a large part of the brain were obtained (Figure 1). The scan also generated excellent 3-D maps of NAA, Cr and Cho (Figure 2).

New Opportunities with 7T MRI Scanner

Cleveland Clinic’s Center for Neuroimaging recently acquired a 7T Siemens MRI scanner to conduct state-of-the-art MRI/MRS studies, making ours one of the first institutions to use a 7T MRI scanner in a neuropsychiatric research setting. The advantages of MRS at 7T include:

- A high signal-to-noise ratio to enhance image quality by decreasing voxel size
- Improved spatial resolution relative to other noninvasive imaging techniques

We will be working to develop MRSI sequences suited for ultra-high fields to take advantage of the increased spatial and spectral resolution they provide.

With our new ability — made possible by ultra-high field strengths — to map metabolite distribution in the entire brain, we hope to gain further insight into the pathophysiology of neurological and psychiatric disorders.

Whole Brain 3-D Magnetic Resonance Spectroscopy: Advancing the Exploration of Neuropsychiatric Disorders

By Amit Anand, MD, and Pallab K. Bhattacharyya, PhD
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REFERENCES


**Key Points**

- Magnetic resonance spectroscopy (MRS) provides an invaluable tool to noninvasively study the neurochemistry of the living brain in neuropsychiatric disorders.

- Whole brain 3-D MRS imaging could potentially be an extremely important tool to study the distribution and concentration of metabolites in the whole brain, providing a comprehensive picture of what abnormalities may underlie neuropsychiatric disorders.

- 7T MRI scanners offer improved signal-to-noise ratio and faster imaging to facilitate whole brain study, overcoming limitations of traditional MR imaging modalities in neuropsychiatric disease. Cleveland Clinic is one of the first institutions to use a 7T scanner in a research setting to study brain neurochemistry in neuropsychiatric disorders.
The need for new therapies for Alzheimer disease (AD) is urgent: Approximately 5.3 million Americans suffer from AD, and that number is projected to rise to 13 to 16 million by 2050 if no means of preventing or treating the disease are found. The need is also broad, encompassing therapies that will prevent AD, delay its onset, slow its progression or improve its symptoms.

Current therapies for AD produce modest improvement in symptoms and a temporary delay in decline. They do not affect the underlying biological processes leading to cell death. Recent advances in understanding the genetics and neurobiology of AD have sparked hope of developing disease-modifying therapies that will interfere with the basic pathology of AD and yield a corresponding clinical benefit. Current investigations are assessing agents with a variety of mechanisms, from affecting the amyloid protein that accumulates in the brain as neuritic plaques, to impacting the tau protein that constitutes neurofibrillary tangles, to preventing cell death.

Targeting the Retinoid X Receptor

Among the agents that appear to affect the amyloid beta protein is bexarotene (Targretin®). This agent was shown in recent studies to dramatically reduce brain amyloid in a transgenic mouse model of AD. Bexarotene is an agonist of retinoid X receptors (RXRs), which regulate cellular processes critical to removing abnormal protein from the brain. In addition, RXRs stimulate macrophages to ingest amyloid and remove it from the brain. These observations spurred considerable enthusiasm in the scientific community. Attempts to confirm the experimental findings have produced inconsistent but still promising results. Two studies reported memory enhancement with bexarotene therapy, but no effect on plaque burden was found; others did show an effect on brain plaques. Bexarotene is uniquely positioned because it is approved by the FDA for treatment of cutaneous T-cell lymphoma, which means there is already substantial knowledge of its effects, side effects, monitoring, formulation and manufacturing. Bexarotene can be repurposed from cancer to AD, enabling accelerated development for use in AD.

BEAT-AD: Breaking Ground on Bexarotene Use for AD

To determine the potential benefits of bexarotene in patients with AD, Cleveland Clinic Lou Ruvo Center for Brain Health has designed an innovative Phase 2A proof-of-concept trial (Figure 1). Known as the BExarotene Amyloid Treatment for Alzheimer's Disease (BEAT-AD) trial, this study will assess the effects of bexarotene on amyloid beta protein levels in the brains of 20 patients with mild to moderate AD. In the study’s initial double-blind phase, 16 patients will receive bexarotene and four will receive placebo for four weeks. In the second phase, all patients will receive bexarotene for an additional four weeks.

The trial comes at an important time in AD research, as the newly approved diagnostic PET tracer florbetapir (Amyvid™) allows visualization and quantification of the presence of amyloid plaques in the brain (Figure 2). Change in amyloid is the primary outcome measure of the BEAT-AD study. The presence of amyloid secures the accurate diagnosis of AD. Removal of plaque amyloid from the brain by bexarotene or other anti-amyloid agents can be monitored with brain PET imaging that incorporates florbetapir. Use of biomarkers as outcomes in clinical trials allows accelerated assessment of compounds worthy of further testing since biological measures are more sensitive to drug-induced changes than are clinical measures.

The BEAT-AD trial also assesses novel clinical outcomes. The measures used in typical clinical trials are incorporated into the BEAT-AD study, including the Alzheimer’s Disease Assessment Scale Cognitive Portion (ADAS-Cog), the Clinical Dementia Rating (CDR), the Alzheimer’s Disease Cooperative Study Activities of Daily Living Scale (ADCS-ADL) and the Neuropsychiatric Inventory (NPI). In addition, advanced cognitive outcomes using computerized assessment are part of the trial design, with Cogstate™ assessments being collected at baseline and after one and two months of treatment.

The primary analysis of the BEAT-AD study is after 30 days of double-blind treatment. A secondary analysis occurs at the end of the two-month trial, when patients will have been treated with bexarotene for two months (those randomized to bexarotene for the first phase) or one month (those randomized to placebo for the first phase). Beyond brain imaging with florbetapir, additional biomarkers are being assessed, including MRI and serum measures of amyloid beta protein and other biomarkers. Biological outcomes, clinical outcomes, and correlations between biological and clinical outcomes are being analyzed.

Bexarotene is known to have toxicities, including a tendency to increase lipid and triglyceride levels and an association with elevated risk of hypothyroidism, cataracts, liver toxicity and anemia. All these potential side effects are being carefully monitored in the BEAT-AD study.

Potential Implications of BEAT-AD

BEAT-AD is the first clinical trial in the world to test bexarotene for the treatment of patients with AD. It will provide an answer as to whether bexarotene, at a dose of 300 mg/day for up to two months, produces a measurable decrease in brain amyloid as assessed by imaging with florbetapir. It will also shed light on the drug’s clinical benefit and safety profile in patients with AD.

If bexarotene has an effect in humans similar to that observed in mice, it will be a significant step forward in AD research. This study exemplifies the advantages of therapeutic repurposing, which is
designed to accelerate the drug development process and reduce the need to constantly invent or discover new compounds by using currently approved treatments that can be applied in new ways. The toxicity of bexarotene may limit its widespread use in AD, but confirming benefits with this mechanism would open a new chapter in AD treatment development.

For more information about the BEAT-AD study, contact Cleveland Clinic Lou Ruvo Center for Brain Health at 702.659.0850.

Florbetapir scans for the BEAT-AD study are being provided by Avid Radiopharmaceuticals/Eli Lilly and Co.

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REFERENCES

Key Points

- No oral drug has been proven effective against brain amyloid accumulation in Alzheimer disease (AD).
- Bexarotene is an agonist of retinoid X receptors, which regulate cellular processes critical to removing amyloid protein from the brain. It is already commercially available for treatment of cutaneous T-cell lymphoma.
- Bexarotene produced a dramatic reduction in brain amyloid in transgenic mice, which was accompanied by improved performance on several measures of cognition and behavior.
- Cleveland Clinic Lou Ruvo Center for Brain Health recently launched BEAT-AD, the first and the only clinical trial examining the efficacy and safety of bexarotene in patients with mild to moderate AD. It employs multiple innovative clinical and biomarker assessments, including use of PET imaging with florbetapir to assess for reduction of brain amyloid.
Despite advances in surgery, radiation therapy and chemotherapy, glioblastoma remains an incurable malignancy with a dismal median overall survival of 15 to 18 months. Preclinical studies have shown that when properly tuned, very-low-intensity, intermediate-frequency electric fields — tumor treating fields (TTFields) — can inhibit the growth of tumor cells. Cleveland Clinic’s Rose Ella Burkhardt Brain Tumor and Neuro-Oncology Center is taking a leading role in studying and using this emerging field of therapy.

The Essentials of Electric Fields

In the laboratory setting and clinical practice, electric fields show a wide range of effects on living tissues. At very low frequencies (< 1 kHz), electric fields stimulate excitable tissues through membrane depolarization. Well-known examples of such effects include nerve, muscle and heart stimulation by electric fields. In addition, low-frequency pulsed electric fields have been claimed to stimulate bone growth and accelerate fracture healing. However, as the frequency of the alternating electric field increases above 1 kHz, the stimulatory effect diminishes.

At very high frequencies (i.e., above many MHz), while the integration becomes even more effective, a completely different biological effect is observed: Tissue heating becomes dominant due to dielectric losses. This phenomenon is the basis for commonly used medical treatment modalities, including diathermy and radiofrequency tumor ablation.

Intermediate-frequency electric fields (i.e., tens of kHz to MHz) alternate too fast to cause nerve-muscle stimulation and involve only minute dielectric losses (heating). Such fields, of low to moderate intensities, were previously considered to have no biological effect. However, a number of nonthermal effects, of minor biological consequence, have been reported even at low field intensities. These include microscopic particle alignment (i.e., the pearl chain effect) and cell rotation. With pulsed, relatively strong electric fields (> 10^3 V/cm and 100-ms pulse length), reversible pore formation appears in the cell membrane, a phenomenon usually called electroporation.

Biological molecules are dipoles (composed of positive and negative charges), and dipole movement can occur with application of an external electric field. In situations in which biological processes require precise spatial alignment, such as mitosis, externally applied electric fields can disrupt this process. This was the hypothesis that led to the initial work evaluating the ability of electric fields to disrupt mitosis in cancer cells.

Preclinical Rationale for TTFields Therapy

In laboratory studies, TTFields demonstrated inhibitory effect in all proliferating cancer cell types tested but had no effect on nonproliferating cells and normal tissues. Interestingly, different cell types showed specific intensity and frequency dependencies of TTFields inhibition.

Two main processes occur at the cellular level during exposure to TTFields: arrest of proliferation and dividing cell destruction. The damage to these replicating cells caused by TTFields was dependent on the orientation of the division process in relation to the field vectors, indicating that this effect is nonthermal.

At the subcellular level, it was found that TTFields disrupt the normal polymerization-depolymerization process of microtubules during mitosis (Figure 1).1 The described abnormal mitotic configurations seen after exposure to TTFields are similar to the morphological abnormalities seen in cells treated with agents that interfere directly or indirectly with microtubule polymerization (e.g., paclitaxel).

TTFields in Action: The NovoTTF-100A System

The NovoTTF-100A System™ (Novocure; Haifa, Israel) is a portable battery-operated device (Figure 2) that produces TTFields within the human body at the site of the tumor using surface electrodes (insulated transducer arrays). The TTFields are delivered to the patient by surface transducer arrays that are electrically insulated so that resistively coupled electric currents are not delivered to the patient. The transducer arrays, which incorporate a layer of adhesive hydrogel and a layer of hypoallergenic medical tape, are placed on the patient’s shaved head. The arrays must be replaced every three to four days and the scalp shaved to maintain optimal capacitive coupling between the arrays and the patient’s head.

All treatment parameters are preset by the manufacturer, so there are no electrical output adjustments available to the patient. The patient and caregiver are taught how to apply and change transducer arrays, change and recharge depleted device batteries, and connect to an external electrical outlet. Patients are fully mobile and can carry on daily activities.

Key Clinical Trial

A prospective, randomized, open-label trial with active parallel control was conducted to compare effectiveness and safety outcomes between patients with recurrent glioblastoma treated with NovoTTF-100A monotherapy (n = 120) and those treated with an effective best standard-of-care chemotherapy (n = 117).2 NovoTTF therapy patients had comparable overall survival to patients receiving the best available chemotherapy in the U.S. today. Patients randomized to the device demonstrated fewer side effects and improved quality-of-life measures relative to the chemotherapy group. This led to U.S. marketing approval of the device by the FDA in 2011 for use as monotherapy for patients with recurrent glioblastoma.
Cleveland Clinic participated in this study, and physicians in our Burkhardt Brain Tumor Center were among the first in the U.S. to prescribe the device for patients with recurrent glioblastoma.

New Trials of Combined Use with Bevacizumab

The Burkhardt Brain Tumor Center is leading an ongoing multicenter study evaluating the efficacy of the NovoTTF-100A System in combination with bevacizumab, an FDA-approved therapy for patients with recurrent glioblastoma. Cleveland Clinic investigators are also leading a planned large international trial of the combination of NovoTTF therapy with bevacizumab for patients with recurrent glioblastoma that has failed to respond to bevacizumab alone. We look forward to the results from each of these investigations.

Key Points

- Alternating electric fields have a range of effects on living tissues. Preclinical studies show that very-low-intensity, intermediate-frequency electric fields known as tumor treating fields (TTFields) inhibit tumor growth by disrupting mitosis in cancer cells.
- These preclinical findings were translated to the development of the NovoTTF-100A System, a portable device that produces TTFields delivered noninvasively within the human body at the tumor site using insulated surface transducer arrays. This device has received U.S. regulatory approval as monotherapy for recurrent glioblastoma.
- Cleveland Clinic’s Burkhardt Brain Tumor Center is leading multicenter trials evaluating the NovoTTF-100A System’s efficacy for recurrent glioblastoma when used in combination with bevacizumab.

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Subarachnoid hemorrhage (SAH) is one of the most devastating forms of stroke. It typically strikes in the prime of life, between ages 40 and 60. Less than half of patients with SAH can return to work at their premorbid level, and many more suffer physical and psychosocial effects that impair function. Currently, the most important predictor of functional outcome after SAH is the early brain injury incurred at the time of aneurysm rupture, yet little is known about the mechanism of insult and no therapeutic treatments for acute brain injury are currently available. New research from Cleveland Clinic’s Cerebrovascular Center and Neurocritical Care Program sheds light on a possible etiology for early brain injury after cerebral aneurysm rupture.

Association of Acute Brain Injury and Post-Aneurysmal SAH Outcome

Admission neurological status — measured by Hunt-Hess grade, from 1 (mild headache or neck stiffness) to 5 (coma) — after SAH reflects acute brain injury and is a better predictor of death or severe disability than any other factor or complication that occurs as a consequence of aneurysm rupture (such as vasospasm). Indeed, sicker patients (Hunt-Hess grades 4-5) have devastating outcomes, with 12-month mortality rates ranging from 43 to 100 percent. Advances in neurocritical care and endovascular treatment of secondary injury after SAH (including vasospasm) have improved outcomes, yet there are no therapeutic options addressing the primary insult, which occurs at the time of aneurysm rupture. A mechanistic understanding of neurological dysfunction after SAH may open new avenues for therapeutic intervention.

Mechanism of Early Brain Injury After SAH: Platelet-Leukocyte Interactions and Infarction

Based on animal studies, one possible mechanism for early brain injury after SAH is platelet-leukocyte interaction leading to microthrombosis and infarction. Aneurysm rupture causes endothelium disruption and exposure of the underlying matrix collagen, which is a potent platelet activator. Additionally, aneurysm rupture results in transiently elevated intracranial pressure with concomitant inadequate cerebral blood flow and, in some circumstances, intracranial circulatory arrest. As a consequence, platelets and leukocytes are activated and aggregate, mimicking the brain injury cascade that occurs after cardiac arrest. These platelet-leukocyte aggregates can obstruct the microcirculation, leading to ischemia and infarction.

We have found evidence of acute platelet activation and markers of inflammation in humans after SAH that correlate with poor admission neurological status (early brain injury) and worse functional outcome. Furthermore, we have investigated early ischemia after SAH using MRI. Examining 61 patients with SAH who prospectively underwent MRI acutely after SAH (within three days of aneurysm rupture), we found that 66 percent had evidence of ischemia. Patients with worse admission neurological status had higher volumes of ischemia. Follow-up MRIs were performed on these patients at days 4-7 and 7-10 after aneurysm rupture. Patients who developed acute ischemia (as shown on MRI) incurred most of their ischemic burden within the first three days after aneurysm rupture (before the onset of vasospasm) and had significantly more ischemia during their hospital stay than those who did not have acute ischemia. Higher volumes of ischemia on MRI were significantly associated with an increased risk of death or severe disability at three months.
Although the pathogenesis of this observed radiographic ischemia acutely after SAH is not well understood, one possibility is that the platelet activation and inflammation we have observed may lead to obstruction of small vessels and to consequent micro-infarctions. This theory is supported by our MRI data, which reveal that 75 percent of acute infarctions are punctate, occurring at the small vessel level, rather than occurring in a segmented vessel distribution. Intracranial circulatory arrest may also contribute to ischemia. This concept is supported by the observation of watershed-pattern ischemia in our and other MRI studies early after SAH.

Future Research: Drilling Down at the Small Vessel Level

Using more sophisticated tests of platelet function and platelet-leukocyte interactions, we hope to drill down on the cascade of events that occur at the small vessel level and lead to acute brain injury. We plan to correlate platelet-leukocyte interactions with MRI evidence of ischemia using sophisticated MRI analysis software. If we determine that platelet-leukocyte interactions are associated with worse early neurological status (implying early brain injury) and MRI evidence of ischemia after SAH, this would imply that therapeutic interventions that attenuate platelet-leukocyte interactions might be clinically useful.

REFERENCES


Key Points

- Evidence of acute platelet activation and markers of inflammation after subarachnoid hemorrhage (SAH) correlate with poor admission neurological status (early brain injury) and worse functional outcomes.
- Prospective MRI studies we conducted acutely after SAH found that two-thirds of patients had evidence of early ischemia; patients with worse admission neurological status had higher volumes of ischemia; and elevated ischemia volumes significantly correlated with death and severe disability at three months.
- We plan future studies to correlate platelet-leukocyte interactions with MRI evidence of ischemia to ultimately help determine whether interventions to attenuate such interactions are clinically useful.
Combatting Concussion at Every Turn: From a Care Path to Boxing Biomechanics and Beyond

By Jay Alberts, PhD

Cleveland Clinic’s Concussion Center, together with collaborating departments and institutes across Cleveland Clinic, is advancing understanding of concussion and its management on an unparalleled number of fronts. Below is a survey of recent developments across various areas of our concussion research and clinical activity.

A Care Path to Curb Practice Variation

We are currently implementing the Cleveland Clinic Concussion Care Path, a comprehensive evidence-based road map to guide clinicians in the management of suspected concussion from initial assessment through long-term follow-up. This tool is one in a systematic series of disease-specific Cleveland Clinic Care Paths designed to improve the value of care by reducing needless and costly variability while maintaining or improving patient outcomes.

In contrast to practice guidelines, our care paths are built on top of guidelines to demonstrate how guidelines can be best implemented and made operational. They share several elements in common:

- Care paths promote continuity and consistency of care by standardizing management of a given condition across disciplines and care settings. This is vital for concussion, as some 372 Cleveland Clinic providers saw at least one but fewer than five patients with concussion during 2012. The Concussion Care Path will allow these providers to draw from a depth of structured concussion expertise not available to them otherwise.

- Care paths are embedded in Cleveland Clinic’s electronic medical record (EMR). Beyond allowing evidence-based care to be delivered without delay, this allows capture and analysis of data on the care delivered and its clinical effectiveness. This will lead to modification of the care path as needed, so that it becomes a living document promoting continuous improvement.

- Care paths are designed to eliminate redundancies and lead to more effective resource use. In some cases this might mean that analysis of the EMR data prompts changes in the types of providers who deliver various types of concussion care and the settings in which that care is delivered.

We expect the Concussion Care Path to be fully implemented across the Cleveland Clinic health system by 2014.

Taking the Concussion App to the ER …

Development of the Concussion Care Path has involved close collaboration with Cleveland Clinic’s Emergency Services Institute, particularly around efforts to make the Cleveland Clinic Concussion (C3) App available in emergency settings for consistent data collection and concussion assessment. As detailed in last year’s issue of this publication (see page 11 at clevelandclinic.org/pathways2012), the C3 App is a proprietary application for the iPad® 2 that promises to change the trajectory of concussion management by enabling objective, affordable, point-of-care assessment of symptoms associated with concussion. (See the sidebar for an overview of how it works.)

While the C3 App has been used for baseline testing among thousands of Northeast Ohio high school and college athletes over the past two years, expansion of its use in emergency rooms through our Emergency Services Institute will allow us to broaden our concussion data-collection efforts into a concussion registry to yield important insights for clinical practice and for generating research questions.

… and to Scale Beyond Northeast Ohio

Expansion of this type has been supported by the April 2013 enactment of Ohio’s Return to Play Law, which is expected to drive a rise in ER visits for concussion assessment in the state. The law requires referees and coaches in scholastic athletics to (1) remove an athlete from play if he or she exhibits signs of concussion or head injury and (2) not permit return to participation until the athlete has been assessed and cleared by a physician or other healthcare provider authorized by the school. Many Cleveland Clinic concussion specialists met with Ohio state lawmakers and testified on behalf of legislation of this type, and the law is an important first step toward raising awareness about proper concussion assessment.

Cleveland Clinic is looking to help meet burgeoning demand for improved concussion assessment by commercializing the C3 App through a spinoff company called iComet Technologies, which has made the app available to athletic trainers and clinicians through the business-to-business app market. We are now pilot testing the app’s use by the athletics program of a rural school district in Rock Valley, Iowa, to assess its utility in a community with few athletic trainers and no physicians who specialize in concussion. We expect this collaboration to be a helpful step toward our goal of making the app usable by schools and providers across the country, ideally in conjunction with the Concussion Care Path.

Our research group working on the C3 App will soon submit for publication initial results on the app’s use by Northeast Ohio school teams. Among the notable findings is a substantial increase in the number of concussed athletes referred for and completing physical therapy.
Our aim is to assess and refine this three-pronged data-gathering approach to build toward prospective longitudinal studies involving large numbers of athletes tracked over years or decades. We hope this approach will prove to be a comprehensive, “one stop” data collection strategy for quantifying the dose of head impact causing neurodegenerative changes.

This investigation complements the Lou Ruvo Center’s landmark Professional Fighters Brain Health Study, which is using annual brain MRIs and other tests in hundreds of professional fighters to examine the cumulative effect of repetitive brain injuries in real time and assess the earliest, most subtle signs of brain injury that correlate with impaired cognition and functioning. That ongoing study, which was profiled in this publication last year (see page 4 at clevelandclinic.org/pathways2012), recently received additional funding to extend its follow-up for another four years.

Next Studies Take Flight with FAA Grant

One of our follow-on studies to the Boxing Biomechanics Study is already getting underway. This investigation, funded by a three-year grant from the Federal Aviation Administration (FAA), aims to determine the level of head impact that causes a human to lose consciousness.

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Cleveland Clinic Concussion (C3) App: How It Works

The C3 App, which was first developed for use in athletes, takes advantage of the iPad’s gyroscope and accelerator to measure motion and acceleration. It works by collecting position and time-series data, along with linear and acceleration data, to assess postural stability and concussion symptoms while an athlete performs balance tests with an iPad attached to the waist. The app also assesses cognitive measures through tasks performed on the iPad screen. Once an athlete undergoes a 15-minute baseline testing session with the app, the app can be deployed by an athletic trainer immediately following a head injury during play to compare results with the athlete’s baseline measures and guide concussion assessment and management.
In funding our study, the FAA is looking to identify the types and degrees of functional deficits present right after a person loses consciousness and how long it takes to recover following various degrees of impact.

The FAA is also looking to identify the types and degrees of functional deficits present right after a person loses consciousness and how long it takes to recover following various degrees of impact. Because boxers and mixed martial artists are the only population in which it is feasible to study the threshold of consciousness loss, our work on the Boxing Biomechanics Study positions us perfectly for performing this research.

We are spending the first 12 months of this FAA study modifying the Intelligent Mouthguard for use in professional fights, which requires placing the device’s battery in the mouthpiece rather than in the headgear, and coordinating use of the Intelligent Mouthguard with the C3 App for the new research questions at hand. The following 12 months will involve collecting data with the modified mouthguard and C3 App from a series of professional fights. The final 12 months will involve data analysis and additional data collection from fights as needed.

A Coordinated Concussion Research Vision

These efforts are further complemented by ongoing Cleveland Clinic work on still other aspects of the concussion crisis, including:

- New findings from our Lerner Research Institute on measurement of the brain protein S100B in blood to assess the effect of repeated blood-brain barrier disruption (see sidebar, next page)
- Use of advanced MRI techniques by Stephen Rao, PhD, and other Neurological Institute colleagues to better understand how the brain changes with concussion (see page 28 of this issue)
- Early efforts in conjunction with Cleveland Clinic Children’s to adapt the C3 App for use in athletes 5 to 12 years old, a population for whom few normative data currently exist

Cleveland Clinic offers a uniquely coordinated institutional vision to help protect the brains of the estimated 1.8 million Americans who suffer a concussion every year. The Concussion Center is proud to be at the center of these efforts, and we look forward to sharing insights from our diverse initiatives to help advance this vision.

Dr. Alberts is Director of Cleveland Clinic’s Concussion Center. He can be reached at 216.445.3222 or albertj@ccf.org.
What’s the Effect of Repeated Blood-Brain Barrier Disruption in Football Players?

One example of Cleveland Clinic’s interest in concussion beyond the Concussion Center is an NIH-funded study published earlier this year by the lab of Damir Janigro, PhD, in Cleveland Clinic’s Lerner Research Institute and colleagues at the University of Rochester.

Janigro’s team studied 67 college football players to test the hypothesis that disruption of the blood-brain barrier (BBB) following head impact, together with the accompanying surge in the brain protein S100B in blood, may cause an immune response associated with autoantibody production.

Though none of the players suffered a concussion during the season studied, transient BBB damage, as measured by serum S100B, was detected — but only in players experiencing the greatest number of subconcussive head hits in a game. Indeed, autoantibodies against S100B were elevated only after repeated subconcussive events characterized by BBB disruption. Serum levels of S100B autoantibodies also predicted the persistence of abnormalities on diffusion tensor imaging, which in turn correlated with cognitive changes. The researchers concluded that:

• Football players may experience repeated BBB disruption and serum surges of S100B even in the absence of concussion.

• The correlation of serum S100B autoantibodies with changes on diffusion tensor imaging supports a link between repeated BBB disruption and risk for future cognitive changes.

Though further study is needed, the S100B blood test used in the study could one day offer a convenient, inexpensive and objective means of quickly assessing the severity of head trauma and whether medical intervention is needed.

The study, which was sponsored by the National Institute of Neurological Disorders and Stroke, is published in PLOS ONE (2013;8[3]:e56805).

Key Points

• The Concussion Center and collaborators throughout Cleveland Clinic are conducting clinical and research initiatives across diverse aspects of concussion assessment and management.

• Our active clinical initiatives include implementation of the evidence-based, EMR-integrated Cleveland Clinic Concussion Care Path and dissemination and refinement of the Cleveland Clinic Concussion App for use in emergency settings and by schools and communities outside Northeast Ohio.

• Our active research initiatives include the Boxing Biomechanics Study, the first investigation to combine imaging studies, behavioral assessment and evaluation of impact dynamics to study the acute effects of head impacts in combat sports.
Robot-Assisted Stereotactic Laser Ablation Under Real-Time MRI:
A FIRST OPERATIVE TECHNIQUE REPORT IN MEDICALLY INTRACTABLE EPILEPSY
Laser ablation under real-time MRI guidance for brain pathology is increasingly being used by neurosurgeons. Since the initial cases in France in 2006 targeting metastatic tumors and subsequent procedures in the United States in 2008 targeting both primary and metastatic brain tumors, surgeons have ablated epileptogenic lesions and radiation necrosis. Epileptogenic areas — including tubers (in tuberous sclerosis), mesial temporal sclerosis (via selective laser amygdalohippocampotomy) (Gross R et al, abstract presented at the 2013 Annual Scientific Meeting of the American Association of Neurological Surgeons), and focal cortical dysplasias and hamartoma — have been treated successfully.

The minimally invasive opening (3.2 mm), small diameter of the laser applicator (1.65 mm), and ease of placement with subsequent short ablation time (usually < 5 minutes) and MRI scanning time (usually < 90 minutes) have allowed procedures to be performed in a safer and more efficient manner compared with open procedures (where deep lesion access would be contraindicated due to access-related morbidity).

Adding Robotic Assistance to Ensure Precision

A key requirement of laser ablation is precise and safe placement of the laser fiber within the intended target. The ROSA™ robot (Medtech Surgical, Newark, N.J.) has been increasingly used to place single or numerous electrodes or catheters into brain targets, with demonstrated accuracy and safety. Additionally, intraoperative MRI allows real-time monitoring of intracranial pathology, enabling treatment to be modified if needed while maintaining a sterile environment and keeping the patient anesthetized. While it is not an absolute necessity for performance of the procedure, intraoperative MRI can assist in these notable ways.

The combination of these three techniques facilitates robot-assisted stereotactic laser placement, with subsequent MRI confirming placement and allowing treatment confirmation. We present here what we believe is the first operative technique report describing the combined use of these three modalities.

Illustrative Case

The patient, a 19-year-old female, had suffered medically intractable focal partial epilepsy since age 9. The epileptogenic zone was localized to the right frontal region using noninvasive data (semiology, scalp EEG, MRI, PET and ictal SPECT) complemented by an invasive evaluation using the stereoelectroencephalography methodology (SEEG). MRI revealed a periventricular heterotopic-appearing lesion that proved to be epileptogenic by intraläsional depth electrode ictal recordings. Given the patient’s 10-year duration of medically refractory epilepsy, treatment options were discussed with the patient, and she elected to proceed with the laser ablation procedure.

Methodology. Working under an IRB-approved protocol at Cleveland Clinic, a preoperative thin-slice MRI was obtained in various sequences (T1, T2, FLAIR). The lesion was clearly visualized using T1-weighted MRI, suggestive of a hypointense (< 1 cm) region adjacent to the right frontal horn and caudate nucleus. This MRI study was uploaded to the ROSA robot, and a plan was created that defined the entry point at the right frontal region as well as the target and a safe pathway that avoided blood vessels (Figure 1).

The patient was anesthetized in the operative suite, which was separated from the adjoining MRI suite by a retractable wall with common ceiling tracks for the IMRIS MRI system (IMRIS, Winnipeg, Manitoba, Canada). The patient’s head was placed in a Leksell® frame (Elekta, Stockholm, Sweden) with left frontal and right posterior posts and pins applied; the frame was affixed to the operative bed. The ROSA robot was moved into position, registered with the patient using surface landmarks (facial features, e.g., nasion, tip of nose, canthi) and verified. The entry point was marked once a satisfactory registration was achieved, and the robot remained locked in position.

After a small region was shaved and prepped around the entry site, a cordless power drill was used to make the scalp “incision” and the hole in the skull (3.2 mm). The dura was coagulated open and entered, and the robot arm was used to determine trajectory and depth. Using an aligning rod through the robot trajectory guide, a skull bolt (Visualase, Houston, Tex.) was placed and secured in the hole. The bolt contains a silicone diaphragm allowing loosening for passage and securing of the laser applicator. The laser applicator (a 980-nm laser fiber with cooling catheter, collectively measuring 1.65 mm in diameter) was passed through this bone screw and advanced just proximal to the distal end of the lesion initially, with a steri-strip applied longitudinally along the fiber to mark the intended depth. With the sterile field maintained, the retractable wall between the operative and MRI suites was opened, and the MRI system was slid into position along the ceiling tracks.
This case illustrates the feasibility of a unique combination of robot, laser and intraoperative MRI to offer minimal invasiveness, minimal duration of treatment and swift recovery — without compromising efficacy.

After confirmation of proper applicator position (see Figure 1) using intraoperative multiplanar images on MRI (Siemens, Munich, Germany), correct trajectory was confirmed and the surgeon elected to advance the fiber to the distal end of the lesion (to optimize lesion coverage, with advancement accomplished in approximately three minutes). Images were acquired to verify optimal position, and ablation began. As a precaution, safety points were designated around the fiber to allow real-time monitoring of heat and trigger a laser shutoff if a higher-than-desired temperature was reached close to the laser applicator or in surrounding healthy tissue. The laser was powered at 9W for approximately 60 seconds. Real-time thermal mapping was superimposed on MRI and refreshed every four seconds (Figure 2). Creation of an approximately 1-cm lesion was confirmed both on intraoperative diffusion imaging and on post-procedure gadolinium-enhanced T1-weighted imaging (Figure 2). The MRI system was slid back into the MRI suite, the laser applicator was removed and the incision was closed using a single stitch (with sterility maintained throughout). Figure 3 shows various intraoperative steps throughout the procedure.

Results. The procedure, from skin incision to end of ablation, was performed in approximately 90 minutes. The laser ablation was performed in less than three minutes, with approximately 45 of the 90 minutes spent acquiring images in the MRI scanner. Approximately 30 additional minutes were spent preoperatively to place the patient in the modified frame and register the robot. Accurate placement of the laser applicator (matching pre-planned trajectories) was achieved using the robotic guidance and confirmed by intraoperative MRI. Post-ablation MRI showed complete ablation of the focal periventricular heterotopic lesion, with an approximately 1-cm ellipsoid lesion created by the applicator. A gadolinium-enhancing rim (Figure 2G) shows the sharp delineation between normal brain and the lesion, with significant drop-off in heat between these areas as planned and described above.

The patient did not suffer any neurological or other complications, and she awoke immediately after the procedure. As the post-ablation scan revealed no bleed, she was transferred to the floor (without intensive
Laser ablation under real-time MRI guidance for brain pathology allows procedures to be performed more safely and efficiently. The addition of intraoperative MRI for real-time monitoring enables treatment modification, if needed, while maintaining a sterile environment.

We present here the first operative technique report, to our knowledge, describing the combined use of laser ablation, robotic assistance and intraoperative MRI. We used these modalities in a 19-year-old woman with medically intractable focal partial epilepsy, achieving complete ablation of the focal periventricular heterotopic lesion without complications.

Although further study is needed, the successful outcome of this case demonstrates the feasibility of combining these three modalities to shorten ablation procedures and recovery time without compromising efficacy.

REFERENCES


Dr. Gonzalez-Martinez is a neurosurgeon and director of the epilepsy surgery fellowship program in the Epilepsy Center and the Department of Neurological Surgery. He also holds an appointment in the Department of Biomedical Engineering. He can be reached at 216.636.5860 or gonzalj1@ccf.org.

Dr. Bingaman is Vice Chairman for Clinical Areas in the Neurological Institute and a neurosurgeon in the Epilepsy Center. He can be reached at 216.444.5670 or bingamb@ccf.org.

Key Points

- Laser ablation under real-time MRI guidance for brain pathology allows procedures to be performed more safely and efficiently. The addition of intraoperative MRI for real-time monitoring enables treatment modification, if needed, while maintaining a sterile environment.

- We present here the first operative technique report, to our knowledge, describing the combined use of laser ablation, robotic assistance and intraoperative MRI. We used these modalities in a 19-year-old woman with medically intractable focal partial epilepsy, achieving complete ablation of the focal periventricular heterotopic lesion without complications.

- Although further study is needed, the successful outcome of this case demonstrates the feasibility of combining these three modalities to shorten ablation procedures and recovery time without compromising efficacy.
Assessments of neurologic function in patients with multiple sclerosis (MS) have traditionally been performed during office visits. However, in a chronic disease such as MS, characterized by an unpredictable course with exacerbations and progression over time, more precise and frequent assessments are needed to guide increasingly complex treatment decisions.

Cleveland Clinic’s Mellen Center for Multiple Sclerosis Treatment and Research, under the leadership of Richard Rudick, MD, together with the team of Jay Alberts, PhD, in the Department of Biomedical Engineering, is addressing this challenge with a set of performance tests developed for the iPad® — the Cleveland Clinic Multiple Sclerosis Performance Test (MSPT) app. The goal is to facilitate assessments in a variety of settings, including the patient’s home. In addition to providing enhanced information to clinicians and researchers, the MSPT app will eventually help empower patients with MS to participate more fully in their own care.

Patient Assessment: The Need for a Better Way

The need for novel assessment tools in MS management is driven by several factors:

· The best-practice model of care for MS is comprehensive management, which involves assessing and monitoring multiple consequences of the disease.

· Treatment options for the disease process and for resulting symptoms and disability are rapidly growing, which leads to increasingly complex decision-making and the need to closely measure treatment outcomes.

· The disease course is unpredictable, requiring management and monitoring to be individualized.

· Healthcare reimbursement is increasingly driven by performance, which requires the ability to routinely generate outcomes data.

The duration and frequency of clinic or office visits currently limit our ability to perform thorough and repeated assessments of functional performance. Furthermore, patients with neurologic disabilities may find it difficult to travel to a medical clinic or may live far from an MS specialist. At the same time, technological advances and progress in measurement science offer opportunities to precisely quantify performance while minimizing the time, personnel and equipment needed.

An App Is Born

These factors prompted development of the MSPT app to enable easy and objective quantification of patients’ neurologic function on an iPad. Using the sensors embedded in the tablet, the MSPT app allows assessment of the following functions across the spectrum of MS disability:

· Walking speed

· Balance

· Upper extremity function

· Processing speed (a cognitive test)

· Low-contrast visual acuity

Validation Underway

Cross-sectional validation of the MSPT is underway among a target sample of 50 patients with MS and 50 healthy controls. To date, data are available for 27 MS patients and 23 healthy controls who completed the testing session. A preliminary analysis showed excellent test-retest reproducibility as well as agreement between MSPT components and corresponding clinician-administered tests. Statistically significant differences were observed between patients and controls on walking speed, upper extremity function and processing speed. Over 90 percent of participants reported that the MSPT was easy to complete, and none reported fatigue from testing.

Future Developments

The MSPT app will provide a validated battery of performance tests that are easy to administer and will generate quantitative results that

Multiple Sclerosis Performance Testing: Novel App Seeks to Enhance Functional Assessment and Empower Patients

By Francois Bethoux, MD
In addition to providing enhanced information to clinicians and researchers, the MSPT app will eventually help empower patients with MS to participate more fully in their own care.

Dr. Bethoux is a physiatrist in the Mellen Center for Multiple Sclerosis Treatment and Research specializing in neurorehabilitation and spasticity management. He can be reached at 216.444.9025 or bethouf@ccf.org.

The validation study of the MSPT was funded by Novartis Pharmaceuticals Corp.

Key Points

- Practical constraints limit clinicians’ ability to perform quantitative functional assessments of patients with MS during routine office visits.

- The Cleveland Clinic Multiple Sclerosis Performance Test (MSPT) app was developed to allow frequent, cost-effective and user-friendly capture of objective measures of neurologic performance across providers and settings — and eventually by patients at home.

- The MSPT is being validated and will be available as an app for the iPad. It is representative of a new generation of tools to enhance MS care and research.
Fibromyalgia: Why a Specialized Interdisciplinary Clinic Makes Sense for Whole-Patient Management

By Sara Davin, PsyD, MPH; Carmen Gota, MD; Brinder Vij, MD; and Judith Scheman, PhD

Interdisciplinary chronic pain management has been the philosophy of the Neurological Center for Pain for the past 34 years. Thousands of patients with fibromyalgia (FM) are treated each year in our center and in the Department of Rheumatic and Immunologic Diseases in Cleveland Clinic’s Orthopaedic & Rheumatologic Institute. Outcome studies from patients with severe, disabling FM in our center’s Chronic Pain Rehabilitation Program have demonstrated substantial improvements in pain, mood and function. These findings led the Neurological Center for Pain and the Orthopaedic & Rheumatologic Institute to begin collaboration in 2012 on development of a specialized Fibromyalgia Clinic, with the goal of providing a disease-based approach for patients with this challenging condition.

Fibromyalgia — Easy to Diagnose, Difficult to Treat

FM is a diagnosis of inclusion, not exclusion. It is suggested by the presence of widespread pain for at least three months in association with fatigue, nonrefreshing sleep, difficulty with memory and concentration, and a constellation of other somatic conditions such as irritable bowel syndrome, migraines, postural orthostatic tachycardia, depression, anxiety and other mood disorders. The physical examination is normal, but tender points are present in about 80 percent of patients and brisk reflexes are also frequently observed.

FM poses significant health economic challenges. Because of FM’s rich associated symptomatology, patients often end up seeing multiple providers. Each specialty initiates a battery of investigations to reassure the patient and physician that no “organic” disease is present.

The cause of FM is unknown, but in many ways it is the quintessential biopsychosocial disorder, with evidence implicating genetic, psychosocial and environmental causation. Some have conceptualized it as an abnormal response to persistent chronic stress leading to excessive and ineffective activation of the sympathetic system and to abnormalities of pain processing at various levels of the nervous system, including peripheral ascending and descending pathways and central sensitization.

The psychosocial challenges in FM require a specialized approach. Recent research suggests a deficiency in self-regulation of thoughts, emotions and social interactions.1 Such deficits in self-regulation impair patients’ ability to cope effectively with FM. Emotional volatility and pain catastrophizing are common and complicate treatment. Passive coping strategies such as isolation and inactivity are often relied on. A history of trauma is not uncommon, predisposing patients to interpersonal difficulties and mistrust of others, including medical providers.

Because patients with FM tend to consume large amounts of healthcare, providers have frequent contact with them. Patients often assume that providers think symptoms are “all in their head” and thus rarely pursue psychological intervention when it is recommended. Psychosocial Factors Figure Prominently

Attention to psychosocial variables is paramount for successful management of FM. There is good evidence for the beneficial role of cognitive behavioral therapy (CBT).2 Recent research also points to the usefulness of psychodynamic therapies and mindfulness-based treatments that target interpersonal relationships and emotional processing and aim to bolster positive affect.3,4 Regular exercise is a crucial modality in the management of FM, but convincing patients of this is a challenge, as they often fear movement and display avoidance behavior. As a general principle related to physical therapy, patients with FM have to “start low and go slow.” Recent research demonstrates that moderate to vigorous physical activity improves long-term clinical outcomes — including psychological health status, health-related quality of life, sleep and cognition — without worsening pain in FM.

Fibromyalgia Clinic: The Rationale for an Interdisciplinary Approach

No single treatment “cures” FM. Medications such as antidepressants (only those that inhibit both serotonin and norepinephrine uptake) and GABA analogs that modulate calcium channels provide only modest pain improvements. This underscores that focusing on treating a symptom in the context of FM, while ignoring the “whole” patient, is typically ineffective. Successful treatment requires an interdisciplinary approach.

In our Fibromyalgia Clinic, care is provided by a team of specialist providers from rheumatology, pain medicine, pain psychology and physical therapy. A unique component is its assessment clinic, where patients undergo medical, psychological and physical therapy evaluation all on the same day. This approach ensures a coordinated treatment strategy.

After the initial evaluation, patients participate in the Fibromyalgia Management Program, which includes:

- Group CBT (assisted by a manual of psychoeducational material used between group sessions)
- Outpatient sessions with the program’s physical therapists

A one-day intensive educational program is an alternate option for out-of-town patients. Patients with severe, disabling FM are referred to the Neurological Center for Pain’s Chronic Pain Rehabilitation Program.

Data Collection — and Expansions — Underway

Data collection is in process for this new interdisciplinary clinic (Table 1). Early impressions are that patients are experiencing a significant improvement in quality of life. Our goals are to continue to develop standardized management strategies for FM, such as those that
incorporate electronic methods of education, coping skills training and exercise tracking.

Because psychosocial factors have been compellingly shown to mediate outcomes in almost every disease (and certainly in all pain-related conditions), the Neurological Center for Pain is currently expanding specialty clinics for other painful conditions, such as abdominal and spine pain.

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Dr. Vij is an associate staff physician in the Neurological Center for Pain. He can be reached at 216.444.0679 or vjb@ccf.org.

Dr. Scheman is Program Director of the Chronic Pain Rehabilitation Program and Program Director of Psychology in the Neurological Center for Pain. She can be reached at 216.444.2875 or schemaj@ccf.org.

**REFERENCES**


**Key Points**

- Failure of the biomedical approach for managing chronic pain conditions such as fibromyalgia is increasingly clear. Interdisciplinary treatment approaches are necessary to ensure successful treatment.

- Cleveland Clinic’s Neurological Center for Pain and Orthopaedic & Rheumatologic Institute collaborated to develop a specialized interdisciplinary Fibromyalgia Clinic in 2012 to meet patients’ needs for a disease-based management approach. Early findings from the Fibromyalgia Clinic’s robust data collection efforts indicate significant improvements in patients’ quality of life.

- Our future goals include further implementation of electronic methods to enhance patient education and exercise monitoring as well as continued expansion of this interdisciplinary approach to specialized clinics for other chronic painful conditions.

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### Table 1. Demographic and Clinical Data for the First 305 Patients in Cleveland Clinic’s Fibromyalgia Clinic Cohort

<table>
<thead>
<tr>
<th>Category</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>87.25% female</td>
</tr>
<tr>
<td>Mean age (range)</td>
<td>44 (36-62)</td>
</tr>
<tr>
<td>Employment status</td>
<td></td>
</tr>
<tr>
<td>Employed (vs. U.S. population*)</td>
<td></td>
</tr>
<tr>
<td>Not employed (vs. U.S. population*)</td>
<td></td>
</tr>
<tr>
<td>Disabled (vs. U.S. population*)</td>
<td></td>
</tr>
<tr>
<td>Retired</td>
<td>4.6%</td>
</tr>
<tr>
<td>Attending school</td>
<td>3.6%</td>
</tr>
<tr>
<td>Overweight or obese (based on BMI)</td>
<td>77.4%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>98.7%</td>
</tr>
<tr>
<td>Widespread pain ≥ 3 months</td>
<td>97.1%</td>
</tr>
<tr>
<td>Feeling of general weakness</td>
<td>87.6%</td>
</tr>
<tr>
<td>Unrefreshing sleep</td>
<td>85.8%</td>
</tr>
<tr>
<td>Mean hours of sleep per night (range)</td>
<td>6 (4-7.5)</td>
</tr>
<tr>
<td>Headaches</td>
<td>82.5%</td>
</tr>
<tr>
<td>Pain worse at rest</td>
<td>81.9%</td>
</tr>
<tr>
<td>Intermittent numbness in hands and/or feet</td>
<td>81.5%</td>
</tr>
<tr>
<td>11 or more tender points on palpation</td>
<td>81.1%</td>
</tr>
<tr>
<td>Concentration difficulty</td>
<td>79.5%</td>
</tr>
<tr>
<td>Faintness or tiredness after hot shower or in hot weather</td>
<td>79.2%</td>
</tr>
<tr>
<td>Increased sensitivity to bright lights, loud noises and/or strong smells</td>
<td>77.4%</td>
</tr>
<tr>
<td>Memory difficulty</td>
<td>75.5%</td>
</tr>
<tr>
<td>History of depression</td>
<td>67.7%</td>
</tr>
<tr>
<td>Urinary frequency</td>
<td>67.5%</td>
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<tr>
<td>Dry eyes and/or dry mouth</td>
<td>67.0%</td>
</tr>
<tr>
<td>Morning stiffness lasting ≥ 1 hour</td>
<td>65.0%</td>
</tr>
<tr>
<td>Mean duration (in min) of morning stiffness (range)</td>
<td>60 (30-180)</td>
</tr>
<tr>
<td>Brisk reflexes</td>
<td>64.4%</td>
</tr>
<tr>
<td>Constipation alternating with diarrhea</td>
<td>61.8%</td>
</tr>
<tr>
<td>Past or present migraines</td>
<td>15.7%</td>
</tr>
<tr>
<td>Prior diagnosis of sleep apnea</td>
<td>15.7%</td>
</tr>
<tr>
<td>Current depression (PHQ-9 score &gt; 10)</td>
<td>88.6%</td>
</tr>
<tr>
<td>Current severe or moderate to severe depression (PHQ-9 score ≥ 15)</td>
<td>45.8%</td>
</tr>
<tr>
<td>Positive screen for bipolar disorder (MDQ score ≥ 7)</td>
<td>21.6%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>41.8%</td>
</tr>
</tbody>
</table>

*According to U.S. Census and Social Security Administration data.

*PHQ-9 = Patient Health Questionnaire-9; *MDQ = Mood Disorders Questionnaire
Deep Cerebellar Stimulation for Post-Stroke Motor Recovery: A New Strategy to Overcome Lingering Limitations

By Andre Machado, MD, PhD

Despite significant improvements in acute care aimed at reducing tissue loss from stroke, there are still hundreds of thousands of patients in the United States alone who become permanently disabled by stroke. To date, post-acute care consists mostly of physical and occupational therapy. While most patients experience at least some recovery, approximately half of patients who suffer a stroke require long-term assistance for activities of daily living. Given current limitations, new technologies are needed to facilitate post-stroke rehabilitation. These may include electrical or magnetic stimulation, stem cell therapies or other emerging technologies.

A New Approach to Targeting Stimulation

In the past decade, major research efforts were dedicated to investigating the effects of cortical stimulation on post-stroke recovery. Despite success in proof-of-principle animal models and demonstration of safety in small patient cohorts, a large randomized study failed to show improvements beyond those achieved with rehabilitation alone.1

We have proposed a different approach for applying electrical stimulation to the brain in an effort to augment recovery. Instead of targeting the cerebellum and its contralateral hypothalamus in an attempt to reverse a chronic diaschisis, our approach is to aim the electrical field at the cortical surface around the stroke, we have chosen to apply deep brain stimulation (DBS) to natural neural pathways that terminate in the perilesional cortex. This approach holds several hypothetical advantages:

• The effects of stimulation will be delivered to cells in specific cortical layers, irrespective of their location within a gyrus. This is an advantage over epidural cortical stimulation, which is likely to reach neurons at the crown of the gyri more efficiently than those in the depth of the sulci. In addition, cortical stimulation can have opposite effects depending on the orientation of neurons in relation to the electrodes,2 a limitation that is obviated if the effects of stimulation are delivered trans-synaptically.

• Depending on the targeted pathway, the effects of DBS can be carried to perilesional areas medial, lateral, anterior and posterior to the infarct core. This would only be possible with very large cortical grids, depending on infarct size.

• The technology for DBS is already very well developed. This is true also for the tools and techniques of implantation.

• DBS can directly target neural pathways associated with post-stroke reorganization at specific “nodes.” This allows for more energy-efficient chronic stimulation compared with large cortical matrices.

Selecting the Pathway

Several neural pathways could be candidates for chronic DBS. Our choice was to target a long-loop neural network directly involved in post-stroke changes. The rationale for targeting the cerebello-thalamo-cortical pathway has been discussed in detail previously.3 Briefly, we based our rationale on the following:

• The well-known massive connections between the cerebrum and contralateral cerebellum and vice-versa

• The functional co-dependence of the cerebral and contralateral cerebellar hemispheres, illustrated by the dramatic metabolic changes of crossed-cerebellar diaschisis

• That patients suffering from reduced cerebellar output have contralateral cerebral hypoexcitability

• That patients with reduced cerebellar function due to crossed-cerebellar diaschisis have worse post-stroke motor outcomes than patients not affected by crossed-cerebellar diaschisis4

• The wide projection of the dentatothalamocortical pathway to the contralateral hemisphere via multiple thalamic nuclei

Hence, stimulation can affect cortical areas spared after large-convexity infarctions. In a very simplistic way, one could explain our approach as reversed or upside-down crossed-cerebellar diaschisis.

Proof of Principle and Current Evidence

Our work began with several open questions, including:

• How should we choose the stimulation parameters that would best enhance cortical excitability?

• Would increased cortical excitability correlate with motor recovery?

• When should stimulation be initiated after stroke?

• Should stimulation be paired with motor training?

Stimulation parameters. To date, DBS therapies for conditions ranging from Parkinson disease and essential tremor to obsessive-compulsive disorder have used high-frequency (> 100 Hz) stimulation. High-frequency DBS is thought to have reversible, lesion-like effects. This is illustrated by the similar results obtained with Vim thalamotomy or Vim DBS in patients with essential tremor or Parkinson disease. However, the goal of our novel therapy is to enhance rather than diminish the cerebellar output. To address the question of stimulation frequency, we used a rodent model of intracortical motor evoked potentials to index cortical excitability. These animals were also
Instead of aiming the electrical field at the cortical surface around the stroke, we have chosen to apply deep brain stimulation to natural neural pathways that terminate in the perilesional cortex.
implanted with contralateral deep cerebellar electrodes. When cerebellar stimulation was set to high frequency, we observed a net reduction of cortical excitability, in agreement with current DBS models. We then tested the effects of various frequencies from 10 to 50 Hz. We found that frequencies between 20 and 50 Hz were associated with increments in cortical excitability but that maximal and sustained results were obtained within the beta frequency range (Figure 1).

First proof of principle. We tested the effects of chronic deep cerebellar stimulation at various frequencies in a rodent model of middle cerebral artery (MCA) infarctions. Stroke was induced by microsurgical ligation of the MCA and temporary occlusion/reperfusion of the common carotid arteries. A nonsignificant trend for greater recovery was observed in animals treated with 50-Hz stimulation but not 10-Hz stimulation. However, animals treated with 20-Hz stimulation (i.e., within the beta band) presented with significantly greater recovery than did animals receiving sham treatment, that is, implanted with DBS leads and connected to stimulation apparatus but not stimulated. In this first test, animals were stimulated during 12 hours of their awake, freely moving cycle but, due to technical limitations, were disconnected from the stimulation system at the time of motor training and testing.

Paired treatment. In a recent evaluation, we changed our outcome measure for the rodent model to the pasta-matrix task. In this assessment, rats reach for pieces of pasta through a small slot, promoting use of the paw weakened by cerebral ischemia (Figure 2). A key advantage is that animals do not have to be disconnected from their stimulation devices during motor training/testing. Animals were divided into two groups: chronic stimulation at 30 Hz during the wake cycle, and sham treatment. In this re-evaluation we found significant improvements in motor function associated with chronic stimulation paired with motor training, indexed with the new task, relative to sham (Figure 3). In fact, treated animals returned to their pre-stroke baseline motor performance. We also found that chronic stimulation was associated with increased expression of synaptophysin in the perilesional cortex. Because synaptophysin is a protein present in presynaptic vesicles, this suggests that stimulation promoted recovery of function and perilesional synaptogenesis. Although these results hint at the possibility that recovery was mediated by greater synaptogenesis, causality has not been proven.

Next Steps: Combining Techniques to Test New Stimulation Paradigms

Our group still has several challenges ahead, including achievement of human translation. Next steps in the laboratory include further evaluation of possible mechanisms associated with motor recovery and testing of new, complex stimulation paradigms. We are currently using a combination of techniques to address these questions, in collaboration with the laboratory of Grahame Kidd, PhD, and Bruce Trapp, PhD, in Cleveland Clinic’s Department of Neurosciences. Further experiments should address the question of optimal timing and duration of chronic stimulation.

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Key Points

- New technologies are needed to facilitate post-stroke rehabilitation. Despite success in preliminary studies, cortical stimulation for post-stroke recovery failed to show improvements in a large randomized trial compared with rehabilitation alone.

- We have proposed a different approach for applying electrical stimulation to the brain to augment recovery from stroke. It involves applying stimulation to natural neural pathways that terminate in the perilesional cortex, namely, the dentatothalamocortical pathway.

- Stimulation of the dentatothalamocortical pathway enhances excitability in the contralateral cortex.

- Evidence from proof-of-principle studies has been encouraging. Stimulation of the dentatothalamocortical pathway significantly improves motor outcomes and markers of synaptogenesis in the rodent model. Further evaluation is needed and ongoing.

Figure 3. Performance on the pasta matrix task over three weeks, during the chronic stimulation period for STIM+ (gray) and STIM− (blue) animals. There is a significant improvement between weeks 1 and 3 and between weeks 2 and 3 in the STIM+ group (**P < .01). By the third week of stimulation, animals in the STIM+ group retrieved significantly more pieces of pasta with the dominant paw compared with the STIM− group (**P < .01). Figure reproduced, with permission, from Machado et al,©2013 Congress of Neurological Surgeons.
Imagine experiencing sudden, brief and uncontrollable episodes of laughing or crying, sometimes at inappropriate moments, up to 30 or more times a day. That’s reality for the estimated 2 million U.S. patients with various brain disorders who suffer from pseudobulbar affect (PBA), also known as emotional lability or pathologic laughing and crying.

Our team at Cleveland Clinic co-led the pivotal multicenter study that formed the basis for the recent FDA approval of the first medication indicated for treatment of PBA, dextromethorphan/quinidine (Nuedexta®). This article reviews the essentials of PBA and the role of this agent in treating PBA in patients with amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS) and other neurologic conditions — as well as potential additional benefits of the drug in these diseases.

PBA: Unclear Pathophysiology, Stark Manifestations

PBA has an unclear pathophysiology but seems to arise from disinhibition of brainstem motor expression due to lesions along the cortico-ponto-cerebellar pathway (Figure 1). It has a high prevalence among patients with a number of neurologic disorders, particularly ALS:

- Up to 50 percent in ALS
- Up to 30 percent in MS, dementia and stroke
- Up to 20 percent in Parkinson disease and traumatic brain injury

When crying is the primary manifestation of PBA, it can often be confused with depression, resulting in misdiagnosis, mismanagement and inappropriate treatments. A major distinguishing feature from depression is that emotional expressions of PBA are usually incongruent or exaggerated relative to the individual’s underlying mood. A person with PBA will laugh when not necessarily feeling happy or cry when not feeling sad. Episodes tend to be paroxysmal, brief (lasting seconds to minutes), frequent, and stereotypical in frequency, duration and intensity.

Episodes of PBA frequently cause distress to patients and caregivers, impaired social and occupational function, embarrassment, social phobia, withdrawal and isolation, and feelings of frustration and humiliation.

First Approved PBA Therapy Emerges

Until recently, antidepressants, including tricyclic agents and selective serotonin reuptake inhibitors (SSRIs), were used off label as the first-choice treatment for symptoms of PBA, but data from well-controlled trials to support their efficacy are sparse.¹ Moreover, tricyclic antidepressants and SSRIs have substantial side effects, especially in the elderly, which can limit their utility for PBA.

In October 2010, the FDA approved dextromethorphan/quinidine for the treatment of PBA, regardless of the condition underlying it, making the agent the first approved therapy for this disorder. The European Medicines Agency (EMA) approved it for similar use in June 2013.

Dextromethorphan (DM) is the active ingredient, whereas quinidine (Q) inhibits the liver enzymes that metabolize DM, which allows therapeutic concentrations of DM sufficient to cross the blood-brain barrier and interact at sigma-1 and glutamate receptors in the brain. Although DM’s exact mechanism of action is uncertain, it is believed to influence glutamate signaling through presynaptic inhibition of glutamate release and postsynaptic glutamate response modulation (Figure 2).

Profile of the Pivotal Trial

The STAR trial (Safety, Tolerability and Efficacy Results of AVP-923 in PBA) demonstrated the efficacy of DM/Q for reducing the rate of PBA episodes in patients with ALS (n = 197) or MS (n = 129).² The study enrolled patients from 64 sites, with Cleveland Clinic enrolling the largest number of ALS patients.

Patients were randomized to 12 weeks of double-blind treatment with DM/Q at one of two dosages (30/10 mg or 20/10 mg twice daily) or placebo, followed by a 12-week open-label phase with DM/Q 30/10 mg twice daily. At 12 weeks, both DM/Q dosages produced clinically and statistically significant improvements relative to placebo in:

- Frequency of PBA episodes as assessed by mean change in the daily PBA episode rate (primary endpoint) and appropriate statistical models
- Severity of PBA as measured by the validated Center for Neurologic Study–Lability Scale (CNS-LS)
- Likelihood of PBA remission during the study’s final 14 days, with half of all DM/Q-treated patients achieving remission

The higher dosage of DM/Q was also associated with statistically significant improvements vs. placebo on measures of social function and mental health. Reductions in manifestations of PBA began during week 1 of therapy and were sustained thereafter. Both DM/Q dosages were safe and well-tolerated. Although the FDA approved only the lower dosage for treating PBA, the EMA approved both dosages.

Beyond PBA: Additional Studies in ALS, MS, Alzheimer Disease

The mechanism of action of DM/Q may also be important in controlling pain, aggression and agitation in dementia, and even...
Neurological Institute are involved in ongoing clinical trials to assess DM/Q for relief of central pain in MS and reduction of aggressive outbursts in Alzheimer disease. Our group is testing DM/Q’s potential to improve speech, swallowing and saliva control in patients with ALS. We look forward to sharing results as they emerge.

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**REFERENCES**


**KEY POINTS**

- Pseudobulbar affect (PBA), or pathologic laughing and crying, is present in an estimated 2 million U.S. patients with various brain disorders, including amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), dementia, stroke, Parkinson disease and traumatic brain injury.

- In late 2010, dextromethorphan/quinidine became the first FDA-approved therapy for PBA based on a trial showing that it significantly reduced PBA frequency and severity in patients with ALS and MS.

- Cleveland Clinic is involved in clinical trials of dextromethorphan/quinidine for relief of central pain in patients with MS; control of aggression in individuals with Alzheimer disease; and improvement of speech, swallowing and saliva control in patients with ALS.
Measuring Brain Activity After Concussion: Insights from Two New fMRI Studies

By Stephen M. Rao, PhD

The brain mechanisms that produce symptoms of concussion and mediate recovery are not well understood. By definition, concussion is distinguished from more severe forms of traumatic brain injury by the absence of observable changes on structural CT and MRI.

Cleveland Clinic’s functional neuroimaging program has applied advanced MRI techniques, such as functional MRI (fMRI), to better understand how the brain changes with concussion. With the use of sophisticated software, brain areas that show increased activity during performance of a cognitive task can be detected and quantified, allowing comparison across clinical groups. We have recently published two fMRI studies that identify patterns of brain activation during the acute (hours), subacute (weeks) and chronic (years) stages following concussion.

First fMRI Study of Brain Activity in Acute Concussion

The first study1 was conducted in collaboration with colleagues at the Medical College of Wisconsin in Milwaukee. More than 3,500 high school varsity football players underwent preseason testing involving cognitive testing and completion of a questionnaire that examined base rate post-concussion symptoms. Over the course of the season, 12 players experienced a concussion and underwent two fMRI scans: at 13 hours and seven weeks after injury. For each of the 12 injured players, an uninjured teammate, matched by education, age and preseason cognitive and concussion symptom scores, also underwent two fMRI scans separated by seven weeks. During the fMRI scan, participants were asked to perform a test of attention and working memory. This is the first fMRI study to measure brain activity during the acute stage of concussion.

Our analyses revealed that 10 brain regions, nine on the right side of the brain, distinguished concussed from healthy athletes. At 13 hours (acute phase), the concussed athletes experienced a slowing in their reaction time along with hypoactivation of their attentional brain networks compared with healthy athletes. At seven weeks (subacute phase), the concussed athletes’ reaction times returned to normal. This was associated with a hyperactivation of the same attentional brain regions (Figure 1).

Several fMRI studies of concussed patients have shown that brain hyperactivation is common during the subacute stage, prompting some investigators to speculate that brain hyperactivation is a necessary compensatory mechanism to allow the concussed athlete to function normally at this recovery stage. Our study is the first to document the evolution from brain hypoactivation to hyperactivation when concussed patients move from the acute to subacute stages. Further research is needed to determine if this shift in brain activation can be used as a diagnostic tool to determine whether an athlete is ready to return to the playing field.

Neural Distinctions Between Blast and Mechanical Concussions

The second study,2 funded by the U.S. Department of Defense, involved collaboration with colleagues at the Baylor College of Medicine in Houston. It was designed to determine if fMRI could detect chronic (one to six years after injury) changes in brain function associated with a concussion. A secondary goal was to determine if the brain activity patterns from concussions experienced by civilians due to a blow to the head is different from those experienced by Iraq and Afghanistan combat veterans due to exposure to explosive blasts. The two concussion groups (military and civilian) were compared with military and civilian control groups. The military controls had combat exposure but had not experienced a head injury or been exposed to a blast. The civilian controls had experienced orthopaedic injuries but had no history of concussion. All four groups underwent a single fMRI study that involved performing a task evaluating inhibitory control processes.

Not unexpectedly, given the length of time since the injury, the two concussed groups performed similarly to the controls on measures of cognitive abilities, suggesting full recovery from a neuropsychological perspective. Concussed individuals also performed normally on the inhibitory control task conducted during fMRI scanning.

Our fMRI results, on the other hand, indicated that both military and civilian concussions produce brain underactivation when participants correctly inhibited their responses. An even more interesting fMRI finding occurred when the concussed individuals were unsuccessful in inhibiting their responses. Blast-related and mechanical concussions demonstrated the opposite brain activity response: compared with their respective control groups, the military concussion group demonstrated hyperactivation while the civilian concussion group showed hypoactivation (Figure 2). Our results could not be explained by the presence of post-traumatic stress disorder or other emotional problems in the concussion groups.

These findings are the first demonstration of a neural basis for distinguishing blast-related from mechanical concussion in humans. More broadly, our fMRI results are noteworthy for identifying a “neural signature” associated with concussion up to six years after injury, even in the absence of demonstrable cognitive deficits. fMRI scans may one day find clinical use as a biomarker for conducting disability assessments and designing rehabilitation programs for treating the chronic sequelae of concussion.
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REFERENCES


Long-Term Functional Outcome After Hemispherectomy in Children: Results of the Largest Single-Center Study to Date

By Ahsan N.V. Moosa, MD; Ajay Gupta, MD; and William Bingaman, MD

Cleveland Clinic’s Epilepsy Center has one of the world's largest experience bases in hemispherectomy for medically refractory epilepsy in children. We recently published the largest single-center experience on seizure outcome after hemispherectomy. Here, we present the functional status of these children at a mean follow-up of six years after surgery.

Hemispherectomy — which involves removal of one hemisphere or, more commonly, disconnection of the hemisphere from the rest of the brain — is an effective treatment option for medically refractory epilepsy due to extensive hemispheric lesions. In a recent study from our center on the longitudinal outcome after hemispherectomy in 170 children (see Suggested Reading), two-thirds of patients were seizure-free at a median follow-up of 5.3 years. Moreover, 80 percent of children in the study either were seizure-free or had major improvement at last follow-up.

Focusing on Function

Apart from seizure outcome, the functional status of these children is a matter of great concern to clinicians and to patients and their families. Before surgery, almost all patients have hemiparesis (with no useful hand function) with or without visual, cognitive or language deficits. Some of these deficits may be expected to worsen in the acute postoperative period. We studied the long-term effect of these deficits on children's ability to ambulate, speak, read and perform at school, and we presented our findings at the 2012 annual meeting of the Child Neurology Society.

Outcomes After Hemispherectomy

Between 1997 and 2009, 186 patients underwent hemispherectomy at Cleveland Clinic. We were able to collect data on the most recent functional status in 125 patients. Seizure outcome of these patients at a mean follow-up of six years is shown in Figure 1. Ten patients with new postoperative nonepileptic spells were excluded from analysis.

Motor outcomes. As noted in several reports, the majority of children were able to walk on follow-up. In our cohort of 115 children, 92 percent were able to walk independently or with assistance (Figure 2). Of the remaining nine patients, five were between 2 and 5 years old, with the potential to eventually attain independent ambulation. Children with bilateral motor deficits (worse on the side concordant with surgery), bilateral MRI abnormalities (markedly worse on the side of surgery) or seizure recurrence were more likely to have poor motor outcomes. When asked about the strength of arms and legs before and after surgery, 54 percent reported no change and 36.5 percent reported worsening of limb strength postoperatively; a small subgroup of patients (9.5 percent) reported subjective improvement in strength, consistent with previous studies. Decreased spasticity in some patients after hemispherectomy is a common reason for the perceived improvement.

Spoken language and reading ability. Spoken language skills and reading ability outcomes are shown in Figure 2. More than two-thirds of children had spoken language skills sufficient for regular conversation, and nearly half of these children had age-appropriate language abilities. Preoperative language delay, bilateral MRI abnormalities and seizure recurrence were associated with poor language outcomes. Age at seizure onset and left-sided surgery had no significant impact on language outcomes in this cohort. Reading abilities were poor in 59 percent of children, and only 18 percent had age-appropriate reading ability. Two-thirds of patients were in mainstream schools, with the majority requiring some form of additional assistance; only five children were in mainstream schools with no assistance.

Behavior and visual symptoms. Based on parental report, 73 percent of patients had minimal to no behavioral problems. The rest had significant problems in home and school environments. Children with postoperative seizure recurrence were more likely to have behavioral problems. Although visual field defect is expected to be present in every patient, families did not perceive it as a major handicap. Patients were accustomed to the defect and were able to take precautions to avoid major mishaps.

Seizure Freedom Improves Functional Outcomes

Seizure freedom emerged as the single most important predictor of functional outcome. Seizure freedom improved the odds of good outcomes in ambulation, behavior, spoken language and reading skills.
Figure 1. Long-term seizure outcome after hemispherectomy in 125 patients. Mean follow-up duration was 6.05 years (± 3.1).

- A reduction in anti-seizure medications in seizure-free patients may have a positive effect on cognition.
- Seizure recurrence may be an indirect marker for an abnormal opposite hemisphere.

This observation may suggest that hemispherectomy improves functional outcomes by providing seizure freedom. However, our study did not have a control group to definitively support such a conclusion.

Cleveland Clinic Hemispherectomy Program

In the past 15 years, more than 230 hemispheric disconnection surgeries have been performed at Cleveland Clinic. We perform four different techniques/variations in hemispherectomy, which are tailored according to patient characteristics to maximize chances for the best seizure outcome and minimize complications. Our youngest patient to undergo hemispherectomy was 2 months and 10 days old, weighing 5 kg.

A team of experienced and dedicated providers, including pediatric epileptologists, epilepsy neurosurgeons, anesthetists, pediatric critical care specialists and several others, strives to ensure the best possible outcome for these children with catastrophic epilepsy. Our continued efforts are focused on making this procedure safe and effective.

SUGGESTED READING


Key Points

- In Cleveland Clinic’s series of 115 children followed after hemispherectomy, 61 percent were seizure-free since surgery, and a total of 81 percent had favorable outcomes (seizure freedom or > 90 percent seizure reduction).

- 83 percent of patients attained independent walking, and another 9 percent walked with assistance.

- More than two-thirds of patients in our series had satisfactory spoken language skills.

- Postoperative seizure freedom favorably affected functional outcome in all domains studied.

Figure 3. Effects of Seizure-Free Status on Functional Outcome Measures

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Inpatient Rehabilitation for Patients with Ventricular Assist Devices: Experience and Insights

By John Lee, MD; Eiran Gorodeski, MD, MPH; Kelly Walters, CNP; and Tiffany Buda, BSN, RN

The rising prevalence of end-stage heart failure in the United States has translated to an increase in the number of patients awaiting heart transplant. Due to the limited supply of donor organs, use of ventricular assist devices (VADs) — as either a bridge to transplantation, a bridge to recovery or destination therapy — has been increasing as well. Cleveland Clinic has an active VAD program, with 59 VADs implanted in 2012. Of the 59 patients who received those VADs, 47 were able to be discharged home, 10 were discharged to our inpatient rehabilitation facility (IRF) on Cleveland Clinic’s main campus and two were sent to a skilled nursing facility.

Recent Rehab Experience by the Numbers

Patients who undergo VAD implantation often become deconditioned as a result of multiple medical issues and long hospital stays. Most require postoperative rehabilitation care. Treatment of VAD patients in the IRF on Cleveland Clinic’s main campus began in 1998. Over the past 12 months, we accepted 17 patients, of whom 13 were discharged to the community and four required readmission to the acute-care hospital. The average length of stay was 16.4 days (range, 4 to 34), and the average change in Functional Independence Measure (FIM) score was 22.5.

Training and Preparation

Treatment of VAD patients requires extensive staff education. All nurses, therapists and physicians at our main campus rehabilitation hospital recently underwent training or retraining over a six-month period to learn about the VAD hardware, the various alarms and how to respond to them, changing the battery and connecting to a power source, mobility issues with the VAD, activity precautions, driveline care, and potential medical complications.

Additionally, clear lines of communication are established between the rehabilitation team and the VAD team.

Experience Breeds Success

Our experience with VAD patients has been very positive. Most patients have achieved significant functional gains and been discharged to the community. Nevertheless, caring for these patients poses challenges, which include the need for daily monitoring of blood pressure and cardiac and fluid status, vigilance for potential medical complications, and thorough patient training and education prior to discharge to the community. The medical complications seen in these patients include bleeding, infections, thrombus of the VAD and stroke.

Throughout the rehab course, the VAD team remains peripherally involved, frequently consulting with the rehab team on management and discharge planning issues. Initial staff trepidation about caring for VAD patients quickly dissipates with increased knowledge and experience in taking care of these patients. The rehab physicians and nurses have become accustomed to managing patients’ medical issues with support from the VAD team; the therapists have become proficient in mobilizing and exercising these patients; and the case managers and psychologists have gained familiarity with addressing the psychosocial and discharge considerations unique to this population.

On the acute-care hospital side, all patients are seen after VAD implantation by a physical and occupational therapy team dedicated to cardiovascular patients, and the physiatrist is consulted for many cases as well.

Future Directions

As our experience with VAD patients continues to grow, we encourage closer and earlier involvement of the physiatry consult service following VAD implantation to facilitate transfer to the next appropriate level of care. Changes along these lines would aim to improve throughput and accelerate admission of appropriate patients to inpatient rehabilitation. We are also using our electronic medical record branching logic to standardize therapy approaches and goals across the acute and post-acute arenas, and we are measuring changes in strength, endurance and balance in addition to FIM score changes.
Case Study: Care Coordination Overcomes Initial Complications in Acute Rehab

A 67-year-old man arrived from out of state for a second opinion on management of his heart failure, including the option of heart transplantation. Before he could return home, his condition deteriorated, and he was admitted through the emergency department. Workup showed severe left ventricular dilation and an ejection fraction of 10 percent. He subsequently had a HeartMate II® LVAD placed as a bridge to transplant.

A Rocky Postimplant Course

His course following VAD placement was complicated and lengthy. He developed respiratory distress, with difficulty weaning from the ventilator, requiring a tracheostomy for a period. Medical management included treatment of pneumonia, *Clostridium difficile* infection and malnutrition as well as the need for anticoagulation due to the VAD, pre-existing factor V Leiden deficiency and deep vein thrombosis.

The patient remained with the VAD service for nine weeks, after which he was admitted to the acute rehabilitation unit with severe muscle weakness, decreased endurance and dysphagia. He was dependent to maximum assist for all activities of daily living (ADLs) and mobility.

Medical Limitations Trump Motivation

During this acute rehab stay, which lasted four weeks, the patient was motivated to participate but limited by progressively worsening dyspnea. The VAD team continued to follow him closely, and an echocardiogram demonstrated distension of the left ventricle without unloading. This finding, along with an elevation in serum lactate dehydrogenase, was consistent with pump thrombosis, so he was readmitted to the acute-care hospital, where he underwent exchange of the thrombosed VAD.

Swift Progress After Stabilization

After a four-week stay in the acute-care hospital, the patient was readmitted to the acute rehab unit. During this admission, his functional progress was rapid, and he was discharged home after two weeks. Arrangements were made with local providers for transition of care back home. Two months after discharge, the patient reported independence in all ADLs and mobility and was able to ambulate short distances in the community with a rolling walker.

A Gratifying Patient Population

VAD patients are medically complex but are a very gratifying population to treat on the inpatient rehab unit. As a result of multiple medical comorbidities, they have complex rehabilitation needs and are able to make rapid, meaningful functional gains if medical stability is maintained (see sidebar). In many cases (e.g., stroke, critical illness neuromyopathy, peripheral neuropathy) these patients qualify under the Centers for Medicare & Medicaid Services’ 60 percent rule, which requires that at least 60 percent of patients admitted have one or more selected conditions in order for the facility to receive payment as an IRF.

More than most other patient populations, VAD patients require the resources of the entire interdisciplinary team working toward the goal of discharge back to the community. When such discharges are made possible, it is a testament to the high degree of coordination among team members and to the immense value inpatient rehabilitation can yield in this population.

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Key Points

- Successful rehabilitation of VAD patients requires adequate training of the interdisciplinary team, awareness of these patients’ concerns and specific management issues, and close collaboration with the VAD team.

- As a result of multiple complex, intercurrent medical conditions, VAD patients have clear rehabilitation needs and are able to make rapid, meaningful functional gains if their medical stability is maintained.

- Inpatient rehab care for VAD patients requires daily monitoring of patients’ cardiac status, blood pressure and fluids; vigilance for potential medical complications; and thorough patient education before discharge.
Studies of Sleep-Disordered Breathing Open New Avenues to Understanding Atrial Fibrillation

By Reena Mehra, MD, MS, FCCP, FAASM

Sleep-disordered breathing (SDB) exposes patients to chronic intermittent hypoxemia and broad swings in intrathoracic pressure. These effects alter autonomic balance, they have untoward impacts on cardiac preload and afterload, and they enhance inflammatory and oxidative stresses, all of which produce a pro-arrhythmogenic milieu (Figure 1). Animal and human studies have identified potential mechanisms by which SDB directly and indirectly alters the functional and cardiac structural substrate for arrhythmogenesis in atrial fibrillation (AF) (Figure 2).

Epidemiologic Evidence of a Role for SDB in AF

Our group has performed several epidemiologic observational studies that have demonstrated statistically significant associations between SDB and AF (odds ratio point estimates, 2 to 4). These associations remained even after we took into account a host of potential confounding factors such as age, sex, race, body mass index and self-reported comorbidities such as hypertension, diabetes mellitus, cardiovascular disease and heart failure.1,2 For example:

- In a study of approximately 600 patients who participated in the Sleep Heart Health Study, we found that those with moderate to severe SDB on overnight polysomnography (PSG) had a fourfold higher odds of AF than did patients without SDB.1

- In a cohort of almost 3,000 older men, we found a stronger association with AF among those with central sleep apnea than those with obstructive sleep apnea, even after controlling for confounding factors.2 In this study, we noted a threshold effect in which patients with moderate to severe SDB (apnea-hypopnea index ≥ 24) had the highest incidence of AF, independent of any self-reported heart failure and cardiovascular disease. Patients who had a central apnea index greater than 3 had a threefold higher incidence of AF, and those with Hunter Cheyne Stokes breathing had an almost fivefold higher incidence.2

- We also examined the temporal relationships between discrete respiratory events and paroxysms of AF.3 This investigation involved a novel application of a case-crossover study design, which is well suited for studying short-lived exposures and outcomes. We found a strong temporal relationship between apneas/hypopneas and paroxysms of AF. Indeed, we noted a 17-fold higher odds of episodic AF during the 90 seconds following an apnea/hypopnea event than after a period of nonobstructed breathing. This finding supports the premise that SDB plays a role in the etiology of atrial arrhythmias.

Implications for Future Research

Now that compelling data have been accumulated regarding aspects of the SDB-AF relationship, future clinical and epidemiologic research should focus on specific areas, including:

- Collection of objective data on cardiac function
- Measurement and analysis of markers of autonomic function, systemic inflammation and oxidative stress
- Examination of both daytime and nocturnal ECGs in an effort to further elucidate pathophysiologic underpinnings
- Reversal of SDB pathophysiology in order to alleviate AF and its associated morbidity and mortality

Two Studies Underway

To overcome knowledge gaps in these areas, our group is conducting two NIH-funded research studies.

Sleep Apnea and Atrial Fibrillation Electrophysiology: Biomarkers and Evaluating Atrial Triggers (SAFEBEAT). This investigation involves examination of paroxysmal AF because it provides an ideal milieu in which to investigate the immediate influences of SDB and to examine its temporal patterns in view of its intermittent nature. In this case-control study, we are comparing 150 patients with paroxysmal AF with 150 controls without paroxysmal AF. Participants are being matched for important confounders such as age, sex, race and body mass index. They will be characterized on the basis of detailed collections of overnight sleep study data, echocardiographic measures, biomarkers and continuous ECG monitoring. With these data in hand, we will have the opportunity to explore the relationships between paroxysmal AF and both obstructive and central apnea. Another goal is to investigate the associations between paroxysmal AF and age in SDB; our earlier work showed that the association of SDB and arrhythmia is stronger in younger patients.1 Moreover, we are examining diurnal variations in paroxysmal AF in patients with SDB in terms of immediate and chronic SDB-related physiologic stresses (i.e., intermittent hypoxia, intrathoracic pressure alterations and autonomic influences). Finally, we are assessing the effects of SDB treatment on paroxysmal AF to inform future randomized controlled trials in this area.

Sleep-Related Respiratory and Electrophysiological Atrial Fibrillation Predictors. The primary goal of this study is to identify PSG-based SDB phenotypes that predict incident AF. We will be investigating the relative contributions of central apnea and periodic breathing vs. obstructive apnea, as well as mediation by inflammation and oxidative stress. Another aim is to identify PSG-derived ECG markers of atrial ectopy, conduction delay and autonomic imbalance, and then to evaluate the markers’ utility as predictors of incident AF. For parts of this study, we will be collaborating with engineers at Case Western Reserve University. Depending on what we find, the results of this study may lead to a shift in the current clinical paradigm by identifying which PSG-based physiologic indices should be included in standard PSG monitoring to forecast arrhythmias such as AF.
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REFERENCES

Key Points
••• Our group has conducted several epidemiologic observational studies demonstrating statistically significant associations of sleep-disordered breathing (SDB) with atrial fibrillation (AF).
••• Subsequent clinical and epidemiologic research should focus on collecting objective cardiac function data; measuring and analyzing markers of autonomic function, systemic inflammation and oxidative stress; examining daytime and nocturnal ECGs; and exploring the impact of SDB pathophysiology reversal on AF and its sequelae.
••• Our group has two NIH-funded studies underway to address some of these research priorities. One study is exploring the relationships of obstructive and central sleep apnea with paroxysmal AF, including the effects of SDB treatment on paroxysmal AF. The other involves identifying polysomnogram-based SDB phenotypes that predict incident AF.

Figure 1. Atrial fibrillation is demonstrated in the ECG channel in the context of severe repetitive apnea/hypopnea associated with oxygen desaturations during REM sleep.

Figure 2. Schematic showing potential mechanisms by which sleep-disordered breathing (SDB) may contribute to atrial fibrillation (AF). Boxes with dashed lines represent the pathophysiologic indices that link SDB and AF (HRV = heart rate variability; HRT = heart rate turbulence; PAC = premature atrial contraction).
The Spine Care Path: An Evolving Tool to Curb Variation from Best Practice

By Daniel Mazanec, MD

Despite increased spending for spine care and a marked rise in the utilization of imaging, interventional and surgical procedures, the functional outcomes of treatment have been declining. Though there is broad consensus among multiple evidence-based clinical practice guidelines for back care, variability in diagnosis and treatment of spinal disorders remains extreme and is influenced by both practitioner specialty and geographic location. The new Cleveland Clinic Spine Care Path has been created to improve the value of spine care by reducing unnecessary and costly variability in management while improving patient outcomes.

From Algorithm to Guides

Developed with multidisciplinary input from medical spine specialists, spine surgeons, physical therapists and pain management physicians, the Spine Care Path is designed to provide an evidence-informed clinical road map to assist practitioners in managing the full range of spinal disorders. The care path began with a work-flow diagram outlining the progression of evaluation and management across the continuum from acute through chronic symptoms, incorporating medical, interventional, surgical, psychosocial and rehabilitation components.

Further evolution of the care path has included development of narrative care path “guides.” The guides for back, neck and radicular pain are designed as clinical manuals for use by the practitioner. They succinctly describe in useful detail the appropriate steps in patient management with supportive rationales and evidence. The guides also provide suggestions for assessment of patient outcome and process measures to be obtained at specific points along the care timeline.

In essence, development of the care path has led to a sharper focus on measuring the value of care, including both patient outcomes and clinical process.

Organizing Principle for Spine Care Delivery

The Spine Care Path and accompanying guides delineate a detailed timeline for delivery of care across the full spectrum of symptoms, involving a wide range of providers: primary care physicians, nurse practitioners and physician assistants, physical therapists, medical and interventional specialists, surgeons, behavioral health clinicians, and rehabilitation specialists.

Development of the care path has raised important questions about the organization of the delivery system for spine care, particularly as we increasingly focus on high-quality, value-based care for populations. The care path serves as the organizing principle for realigning our services — providers and locations — to provide the highest-quality care in a timely manner to patients at all points along the continuum.

Among the issues we are addressing is the need to match appropriate clinicians to patients at various stages of care. For example, acute back pain is common and generally resolves with simple therapy. For patients without red flags, imaging is rarely required. Providing such patients prompt access to care with back education and advice on activities to try may be best achieved using physical therapists or nurse practitioners as entry-level providers. When back pain persists, the care path defines when referral to medical spine specialists, spine surgeons or behavioral health professionals is indicated.

As we are increasingly expected to manage the care of large populations, the care path provides a framework for defining the best mix of providers and required support services and locations to address patients at the various points along the spine care continuum.

Documenting Outcomes and Process Through the EMR

Implementation of the Spine Care Path provides a great opportunity to develop a continuous quality improvement model for spine care. By capturing patient outcome measures in various domains — including pain, function and mood — as well as defined process measures such as imaging use and appropriate referrals, the care path is designed to provide information on the clinical effectiveness of treatment. The ability to capture and analyze these data and modify care as required is facilitated by integration of the care path into the electronic medical record (EMR).

In the Center for Spine Health, patient-reported outcomes — including the nine-item Patient Health Questionnaire (PHQ-9) for mood, the Pain Disability Questionnaire (PDQ) for function and a numerical pain score — are captured at each visit through Cleveland Clinic’s Knowledge Program® and recorded in the EMR (the Knowledge Program is an interactive database that elicits patient-reported validated outcome measures throughout the course of care). Through
use of the care path, important clinical data elements have been identified for inclusion in structured documentation to be embedded in the EMR. These retrievable data sets will facilitate retrospective study of the process, the cost of an episode of care and the episode’s impact on clinical outcomes.

**Continued Refinement: ‘Bolt-Ons’ and Next Steps**

Ongoing evolution of the Spine Care Path includes extending, refining and standardizing treatment limbs such as physical therapy or specialty referrals through what we call “bolt-ons” to the original workflow algorithm. Physical therapy provided for spinal disorders varies from application of passive modalities including heat, massage and traction to active exercise programs ranging from core strengthening to mechanical diagnosis and therapy (MDT, or the McKenzie method). The bulk of evidence suggests that active exercise programs are superior to passive modalities, but comparisons are lacking. Using a best-evidence model, we are developing a standardized physical therapy approach to managing back pain. In addition to physical therapy, bolt-ons are currently in development for emergency department patients (Figure 1), patients with vertebral compression fractures and surgical patients.

The Spine Care Path is now being piloted at a couple of family health centers in the Cleveland Clinic health system. We are monitoring its operation in real-world practice and collecting information on resource utilization for comparison with pre-implementation levels. We look forward to sharing and applying our observations and continuing the refinement of this dynamic management tool.

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Key Points

- Recent evolution of the Cleveland Clinic Spine Care Path includes introduction of narrative care path guides and “bolt-ons” to add detailed recommendations in areas such as emergency care and postsurgical care.

- The care path serves as a framework for defining the best mix of providers, support services and treatment locations to optimize value and patient outcomes across the spine care continuum.

- Integrating the care path into the EMR provides an ideal opportunity to develop a continuous quality improvement model for spine care through the ability to capture, analyze and modify care practices.

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A Smartphone Companion to the Spine Care Path

The Cleveland Clinic Spine Care Path will soon be complemented by a new Cleveland Clinic smartphone application (working name: MySpine) that patients with acute back pain can use as a self-care tool in the early stages of management (in the absence of red flags). The app, developed for both the iOS and Android operating systems, includes the following:

- Educational content about back pain
- Tools for daily pain monitoring and incident reporting
- Videos and images demonstrating recommended exercises
- A post-exercise survey
- Data reports for progress assessment
- Tools for appointment scheduling and clinician messaging

Designed as a companion to the care path during a patient’s first six weeks of management, the app is currently in beta testing.

By capturing patient outcome measures in various domains through integration in the EMR, the care path is designed to provide information on the clinical effectiveness of treatment.
How Much Change Is Enough to Matter?  
Determining Minimal Clinically Important Differences for Health Status Measures

By Sandra D. Griffith, PhD; Deborah M. Miller, PhD; and Irene L. Katzan, MD

With more than 150 different patient health status questionnaires in use across Cleveland Clinic and similar health systems, simply knowing the difference in scores between two time points does not provide sufficient information. Consider a five-point improvement on a scale between a patient’s initial and follow-up visits. Conclusions about the importance of this change will differ depending on whether the scale ranges from 1 to 20 or 1 to 100 as well as on the distribution of patient scores and the content of the questions. How do we filter out the noise to find true changes in patient health rather than simply artifacts of the measurement tool? Even if a change is statistically meaningful, is it noticeable or important to the patient or provider? These questions underlie the concept of minimal clinically important difference (MCID), or the smallest change in a health status measure (HSM) required for a clinically meaningful difference.

As Cleveland Clinic’s Neurological Institute grapples with these questions, we increasingly draw on our Knowledge Program Care Path (KPCP) data collection system, a scalable platform developed by Cleveland Clinic for collection of data from both patient and provider. Patient-reported data obtained through the KPCP are immediately available within the electronic health record for use in clinical encounters. These data are also stored in a database and available for aggregate analyses. Now in its seventh year, the KPCP will soon reach the milestone of collecting HSM data from 1 million patient visits. Armed with an unprecedented number of measurements providing a comprehensive view of patient health, clinicians and researchers face the challenge of interpreting these data to describe patient populations, aid medical decision-making and evaluate care effectiveness. In addition to defining a patient’s health status at a single visit, the KPCP allows us to follow patients over time to provide crucial information on the progression of their health.

This article summarizes the essentials of MCID and how the KPCP is helping us evaluate, refine and apply various approaches to MCID assessment.

Distributional Approaches to MCID

Distributional approaches consider the statistical properties of a given instrument for measurement. Through the KPCP, we are using the large numbers of patient visits with HSM data collected during routine clinical care to better understand the measurement error inherent in HSM instruments. We are conducting studies to estimate the minimal detectable change (MDC) threshold of several HSMs, derived from the standard error of the measurements. If a difference in an HSM is above the MDC threshold, we can proceed with confidence that it is likely a true change and not simply noise from the measurement scale; however, we still need to determine whether the change is clinically important.

Anchor-Based Approaches to MCID

Clinical criteria for MCID rely on anchor-based methods, where an external criterion indicates clinically important changes. The external criterion must be valid for determining the change of interest and have good correlation with the target instrument. The KPCP collects global rating of change (GRC) questionnaires in tandem with some HSMs. These questionnaires ask patients or providers to rate the difference in the patient’s status with respect to a specific health domain (e.g., pain, depression, functional status) since the patient’s previous visit. External anchors, such as the GRC, provide us with metadata about the scales themselves, allowing detection of how much change is required for patients or providers to take notice. We are conducting analyses using KPCP data to link small, moderate or large changes, as described by GRC scales, to numeric differences on HSM scales.

Applying a Mixed-Methods Approach

We are also pursuing focused research studies to generate new evidence that may not be attainable using only data collected through routine clinical care. With this goal in mind, we recently undertook a mixed-methods approach for establishing MCID by anchoring expert judgment of clinical severity to patients’ perceptions of the severity of their HSM scores. We implemented this approach in our multiple sclerosis clinic within the item response theory (IRT)-based HSM platform Neuro-QOL, using four of the assessment domains (upper extremity, mobility, sleep and fatigue).

The first phase of this implementation involved a qualitative process adapted from educational standard setting, which differentiates examinees from either passing or failing a given test. Two expert panels, one of patients and another of clinicians, were presented with multiple clinical vignettes consisting of sets of five items and the corresponding IRT-predicted responses for each item at successively more severe levels of the Neuro-QOL HSMs (0.5 standard deviations apart). Working individually and then as a group, panelists designated transition points between the vignettes where they thought the threshold was between “no problems,” “mild problems,” “moderate problems” and “severe problems” for each HSM.

During the next phase, which is quantitative, we will validate the expert anchors by administering the four Neuro-QOL HSMs through the KPCP to 1,000 patients with multiple sclerosis and asking them to rank the severity of their symptoms between “no problems,” “mild problems,” “moderate problems” and “severe problems.” Congruence between the expert anchors and patient self-report will indicate whether we have established meaningful transition points for each of these measures.
As the Neurological Institute grapples with what constitutes a clinically meaningful change in health status measures, we increasingly draw on our Knowledge Program Care Path, a scalable platform developed for collection of data from both patient and provider.

Implementing MCID in the Electronic Health Record

In our role as a learning healthcare system, we plan to implement MCID findings based on evidence generated here at Cleveland Clinic and elsewhere. As a first step, we are developing strategies to communicate changes in HSM results to providers in the context of measure-specific MCIDs. This will provide clinicians at the point of care with visual information to help them determine the significance of changes in patient health over time. Figure 1 shows a potential display to be seen by providers in the electronic health record, giving a visual representation of the patient's trajectory and signifying clinically important changes with an asterisk. Once implemented, we will evaluate its effectiveness and adjust strategies, as necessary, to ensure continual improvement.

Key Points

- The concept of minimal clinically important difference (MCID), or the smallest change in a health status measure required for a clinically meaningful difference, takes on growing importance with increased monitoring of health status measures.

- Cleveland Clinic’s Neurological Institute is drawing on its Knowledge Program Care Path data collection system to evaluate and apply various approaches to MCID assessment, including distributional and anchor-based methods.

- Our plans to implement MCID findings include strategies to communicate changes in health status measures with visual information at the point of care to help clinicians determine the significance of measure-specific changes over time.

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Figure 1. Example of a potential provider display that indicates whether a clinically significant change in health status measure score has occurred since the patient’s previous visit.
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AUGUST 18-22, 2014
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Cleveland Clinic Gamma Knife Center, Cleveland, Ohio

FEBRUARY 8-9, 2014
Shaping the Management of Parkinson’s Disease: A Comprehensive Review of Discoveries and Clinical Trials
Course Directors: Hubert Fernandez, MD, and Michael Schwarzschild, MD, PhD
Vdara Hotel, Las Vegas, Nev.

FEBRUARY 21-23, 2014
Seventh Annual International Symposium on Stereotactic Body Radiation Therapy and Stereotactic Radiosurgery
Course Directors: Lilyana Angelov, MD; Gene Barnett, MD; Edward Benzel, MD; Samuel Chao, MD; John Suh, MD
The Naples Beach Hotel & Golf Club, Naples, Fla.

MARCH 8-9, 2014
Recognizing Parkinson’s Disease and Its Look-Alikes: 4th Annual Video and Case-Based Weekend Symposium in Movement Disorders
Course Director: Hubert Fernandez, MD
Global Center for Health Innovation and Cleveland Convention Center, Cleveland, Ohio

MARCH 10-12, 2014
Wake Up to Sleep Disorders
Course Directors: Nancy Foldvary-Schaefer, DO, MS, and Tina Waters, MD
Embassy Suites Cleveland – Rockside, Independence, Ohio

APRIL 5, 2014
Advances in Alzheimer’s Disease: An Update
Course Directors: James Leverenz, MD, and Jeffrey Cummings, MD, ScD
Marriott Cleveland East, Warrensville Heights, Ohio

MAY 4-9, 2014
World Spine VI (May 4-6)
Cleveland Spine Review — World Spine Jamaica (May 7-9)
Course Directors: Edward Benzel, MD, and Mehmet Zileli, MD
Hilton Rose Hall Resort, Montego Bay, Jamaica

JULY 10-15, 2014
Cleveland Spine Review
Course Directors: Edward Benzel, MD; Doug Orr, MD; Richard Schlenk, MD; Marc Eichler, MD; Greg Trost, MD
Lutheran Hospital, Cleveland, Ohio

AUGUST 1-3, 2014
2014 Neurology Update — A Comprehensive Review for the Clinician
Course Directors: Jinny Tavee, MD, and Alex Rae-Grant, MD
Ritz-Carlton, Washington, D.C.

OCTOBER 5-11, 2014
International Pediatric Epilepsy Surgery Symposium
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