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On the cover: Figure shows the characteristic morphology of mesenchymal stem cells in culture.
Dear Colleagues,

In 2010, Cleveland Clinic Lerner College of Medicine graduated its second class of physician-investigators. Reflecting on this phase of his medical education, a newly minted neuroscientist explained that he had entered the field because he considered it “the Wild West of medicine.” That comment should resonate with those of us who share his enthusiasm.

Within the Neurological Institute, we are rapidly mobilizing the human and technical resources to probe the diseased brain and advance our understanding of pathologies such as epilepsy, Alzheimer’s disease and multiple sclerosis. In this issue of Pathways, we feature some of our most promising work.

- **Jeffrey Cohen, MD**, from our Mellen Center for Multiple Sclerosis Treatment and Research outlines a pilot study of the safety and tolerability of autologous mesenchymal stem cell transplantation in patients with relapsing forms of MS. Dr. Cohen heads a team that will isolate stem cells from subjects’ bone marrow, then culture-expand and reinfuse them.

  It is hoped that these primitive cells will migrate to damaged sites in the nervous system, and will limit inflammation and encourage tissue repair. No formal trials of this therapy in MS patients have been published.

- **Andre Machado, MD, PhD**, received a National Institutes of Health New Innovator Award and grant to study a novel approach for managing severe, refractory central thalamic pain syndrome. Given that neurostimulation to modulate the somatosensory sphere of chronic central pain has largely failed, this study will evaluate whether modulation of the affective component can reduce pain-related disability.

  Researchers will target the ventral anterior limb of the internal capsule and the adjacent ventral striatum with deep brain stimulation, marking the first time DBS will be applied in this brain area for thalamic pain syndrome.

- Through our Knowledge Program®, our interactive clinical patient database, we have collected data on some 3,000 epilepsy patients who completed validated health status questionnaires. An algorithm developed by George Tesar, MD, alerts clinicians when patients’ responses suggest depressive symptoms. In our Epilepsy Center, Lara Jehi, MD, has spearheaded analysis of the data on depression. This work, which will soon be reported fully, raises intriguing issues.

  First, it highlights the significant prevalence of depression in the epileptic population, thus increasing awareness of this problem. Second, the research documents improvement of depressive symptoms following appropriate medical or surgical care of the epilepsy. The third and most captivating finding is that depression is as significant as seizure severity in defining quality of life in epilepsy patients.

  Balancing these accounts is a thoughtful piece from Cynthia Kubu, PhD, and Paul Ford, PhD, on the ethics of control and consent in deep brain stimulation for Parkinson’s disease. Dr. Kubu, a neuropsychologist, and Dr. Ford, a bioethicist, seek to better understand patients’ goals and expectations in functional neurosurgery.

  Their research offers us a timely reminder in an environment of rapid-fire discovery. Life is exciting out here on the neurological frontier, but our drive to push the boundaries must forever be coupled with an acute awareness of the patient’s best interests.

I hope you find this issue of Pathways informative. Your comments are always appreciated.

Sincerely,

Michael T. Modic, MD, FACR
Chairman, Cleveland Clinic Neurological Institute
A First-Time Study of Autologous Mesenchymal Stem Cell Transplantation in Multiple Sclerosis Patients

By Jeffrey Cohen, MD

In multiple sclerosis (MS), we suspect the body's immune system attacks healthy tissue, or some type of infection promotes inflammation. Although several available treatments can reduce inflammation in these patients, we have no intervention to repair the damage to the central nervous system. In a Phase I study funded with a four-year, $2.75 million grant from the U.S. Department of Defense, Cleveland Clinic will lead an assessment of the safety and tolerability of autologous mesenchymal stem cell (MSC) transplantation to reduce inflammation and promote tissue repair in patients with relapsing forms of MS.

New stem cell therapies that promote healing could potentially mitigate relapsing and remitting symptoms, lessen the likelihood of permanent nerve and brain damage, and provide a better understanding of the mechanisms behind MS.

Stem Cells from Bone Marrow

Our pilot study will be conducted by the Mellen Center for Multiple Sclerosis Treatment and Research in collaboration with the Center for Stem Cell and Regenerative Medicine, a research consortium comprising investigators from Cleveland Clinic, Case Western Reserve University, University Hospitals Case Medical Center, The Ohio State University and the biopharmaceutical company Athersys, Inc.

We are recruiting 24 participants, ages 18 to 55, divided roughly evenly between patients with relapsing-remitting MS and those with secondary progressive/progressive relapsing MS. Patients will not be enrolled simultaneously; only a few will be studied at a time. MSCs will be isolated from patients' bone marrow, culture-expanded and reinfused.

While MSCs exist in fat and other tissues, bone marrow-derived MSCs are the most extensively studied and best characterized. Our research partners already have experience with transplantation of MSCs from bone marrow. These cells appear nearly as pliable as fetal stem cells, without some of the associated practical and ethical issues.

Following a two-month culture period to increase the number of MSCs, we will inject the purified cells intravenously into each patient, who will then be monitored for six months. Because our subjects will receive their own cells, there is no need for immune suppression and little worry about rejection.

No Comparable Studies

We believe the cells that we reinfuse in our subjects will migrate from the blood to damaged regions in the brain or spinal cord. In laboratory studies, MSCs have demonstrated this ability to travel to sites of inflammation or injury, where they have augmented intrinsic repair mechanisms.

Although MSCs have been widely researched, no formal trials in MS patients have been published. These cells are known to support formation of blood cells and to participate in the development of connective tissues. Even so, debate surrounds their primary role. Some researchers have theorized that MSCs also limit inflammation and damage while creating a milieu for repair. Through this study, we hope to gain a fuller understanding of their functions in the body.

The study also provides an opportunity to learn whether an autoimmune disorder such as MS affects stem cell function. It could be that stem cells from patients with MS are compromised. Little research has been done to explore how stem cells function in people with autoimmune disorders or how stem cells from these patients could impact treatment options.

Safety Monitoring Is Foremost

MSC transplantation in several disorders appears safe and well tolerated. However, experience in MS and other autoimmune disorders is very limited. Therefore, we will adhere to strictly defined safety measures from each patient's screening visit onward.

Hypothetically, infusion could provoke a negative immune reaction. Or, the cells could cause an infection or clump together, creating a blockage in the lungs. Another unlikely occurrence is ectopic tissue formation. If the cells moved to the brain and transformed into bone instead of nerves, for example, transplantation could be deleterious.

We will perform testing—to include adverse event review, concomitant therapy review, vital signs, oxygen saturation, general exam, blood chemistry, hematology and urinalysis—at screening, baseline and regular follow-up visits throughout the six-month monitoring period. Chest X-rays, EKGs, neurologic assessments and serum pregnancy testing for female participants will also be administered.

We will adhere to precise guidelines for freezing, thawing and injecting the stem cells. Following infusion, patients will be monitored for six
Typical MRI findings in multiple sclerosis are shown here. In the MSC trial, routine and advanced MRI techniques will be used to monitor MS disease activity and changes in the extent of brain tissue damage.

hours. If any allergic reactions, breathing difficulties or other acute problems develop, the infusion center is equipped to treat these complications immediately.

Immunological Effects

A unique aspect of this study is the significant amount of immunological testing that will occur. MSCs have a wide range of effects that decrease the hyperactivity of immune cells in MS. Working with collaborators at Montreal Neurologic Institute, we will examine the immune reactivity to myelin and the regulatory functions of the immune cells in the blood. We will also test whether immune cells in the blood of recipients are more or less active after MSC infusion.

Finally, we will compare MSCs from persons with and without MS to determine whether MSCs from patients with autoimmune disorders behave differently. While this is not the primary goal of the study, we believe it will enhance our understanding of MS and stem cells.

Jeffrey Cohen, MD, is Director of Experimental Therapeutics at Cleveland Clinic Mellen Center for Multiple Sclerosis Treatment and Research. His specialty interests include multiple sclerosis, neuroimmunology and clinical trials. He can be contacted at 216.445.8110 or cohenj@ccf.org.

Cleveland Clinic Team Assesses Claim of Venous Occlusion in MS

Cleveland Clinic’s Mellen Center for Multiple Sclerosis Treatment and Research is one of seven sites in the United States and Canada that are conducting research projects to investigate the controversial hypothesis linking chronic cerebrospinal venous insufficiency (CCSVI) with multiple sclerosis (MS).

With a grant of more than $570,000 from the U.S. National MS Society, a multidisciplinary team led by Mellen Center Medical Director Robert J. Fox, MD, is seeking to evaluate preliminary findings from an Italian study suggesting that venous stenosis in the veins that drain the brain and spinal cord may contribute to nervous system damage in MS. This theory, which emerged from research by vascular surgeon Paolo Zamboni of the University of Ferrara and colleagues, needs independent verification.

The Zamboni team went on to an unblinded, open-label study in which balloon angioplasty was used to widen MS patients’ veins. Researchers reported that the treatment was effective and the complication rate low.

To test the CCSVI hypothesis of MS pathogenesis, Dr. Fox’s team will evaluate 90 individuals with various forms of MS and 80 control subjects without MS. The team is using the same Doppler ultrasound techniques used in the original study as well as MR venography, MRI scans of the brain and neurological examinations.

Most of the MS patients have already been followed for 10 years in a longitudinal clinical and MRI research study, so the prospectively collected data will be used to compare the evolution of MS with venous abnormalities.

To distinguish whether venous abnormalities are from brain atrophy and not specifically from MS, researchers are comparing the MS group with people who have brain atrophy from other causes. Investigators also are examining neck and spinal cord tissue obtained at autopsy from MS patients and non-MS controls to evaluate for pathologic changes in the venous tissues.

The U.S. and Canadian MS societies have committed more than $2.4 million in support of the seven research projects, which have a two-year term.
Assessing the Efficacy of Cognitive Training and Exercise Training in Elders At Risk for Alzheimer’s Disease

By Stephen Rao, PhD, ABPP-CN

At diagnosis, patients with Alzheimer’s disease (AD) exhibit significant brain tissue atrophy and disruption of brain circuitry. Treating patients at this stage does little to improve cognitive function and slow disease progression. Therefore, finding interventions that can prevent cognitive decline in healthy older individuals is a major focus of AD research. Two interventions—cognitive training (CT) and physical exercise training (ET)—have received considerable attention in the medical literature because they are low risk and have been shown to improve cognitive functioning in asymptomatic older adults. These interventions are the focus of a clinical trial, currently under way at Cleveland Clinic Lou Ruvo Center for Brain Health, assessing their efficacy in older adults at risk for AD.

To date, studies of the effects of short-term CT and ET interventions on cognitive abilities have targeted non-specific groups of elders. In this population, cardiorespiratory fitness and aerobic ET have been shown to improve cognitive performance, especially of tasks that involve memory functions affected by age. Correlational studies have observed that physically active older adults show less brain tissue atrophy, greater cortical plasticity and greater cognitive efficiency. Our research has observed even more pronounced effects of physical activity on brain function in healthy older adults at risk for AD. The positive effects of physical activity are also supported by animal studies, which have demonstrated that physical activity induces hippocampal angiogenesis and neurogenesis.

Several large prospective cohort studies have indicated that more frequent participation in cognitively stimulating activities is associated with reduced risk of development of AD and other forms of dementia in cognitively intact older adults. In controlled CT intervention studies, which have used regimens of standardized cognitive exercises, cognitive improvements have been reported in healthy older adults.

Comparing ET and CT in At-Risk Adults

Funded by an ARRA Challenge Grant, our Cleveland Clinic Neurological Institute study is a 12-week, four-arm, randomized, controlled clinical trial to compare the neural and cognitive efficacy of CT, ET and combined training (CT + ET) relative to an Active Control (AC) that will receive educational and flexibility training (to control for the ET and CT conditions). To date, no study has determined if ET and CT affect neural function recorded during the performance of cognitive tasks, and no controlled clinical trial has directly compared CT and ET as interventions for improving cognitive function in healthy older adults.

The study’s 96 subjects, aged 65 to 85, are healthy and cognitively intact but physically inactive. All are at risk for developing AD based on a positive family history. This is the first study to focus on this population. Subjects will undergo genetic testing to detect the presence of the APOE ε4 allele, which is associated with the development of AD. At present, age, family history and the APOE ε4 allele are the best, imperfect, predictors of cognitive decline in non-demented individuals.

The three primary intervention groups will receive either CT, ET or CT + ET. The exercise intervention will consist of 40 aerobic activity sessions, which will progress to 50 minutes a day, four days a week at an intensity level of 60 to 70 percent of heart rate reserve. The 40 CT sessions are based on a commercial structured program designed to improve central sensory system function. Recent studies suggest this type of program is more effective than direct strategy instruction because it not only improves cognitive abilities but also generalizes to a wide range of everyday life activities. The combined intervention will include 20 sessions each of ET and CT.

Measuring Intervention Efficacy

The primary outcome measure of intervention efficacy will be task-activated functional magnetic resonance imaging (fMRI). In a previous study (reported in the 2009/2010 issue of Neuroscience Pathways), we investigated task-activated fMRI as a biomarker for identifying brain changes in older adults with AD risk factors.

In that study, we administered a famous-name recognition task to cognitively intact elderly participants with and without AD risk factors (APOE ε4 and family history) while they underwent fMRI screening. The results showed that semantic memory for person identity activates several key brain areas (hippocampus, posterior cingulate, anterior cingulate and temporoparietal regions) that are vulnerable to the earliest pathological changes in AD. Task-activated fMRI was reliably sensitive to brain activity in individuals with AD risk factors, making it particularly useful for evaluating the effects of interventions on neural functioning. In another study, we showed that task-activated fMRI at study entry can predict cognitive decline after an 18-month interval (see Figure 1).
Our current study of CT and ET is the first to use fMRI to assess intervention efficacy. We hypothesize that the primary training groups (CT, ET and CT + ET) will exhibit a significant increase in brain activity relative to the AC group after 12 weeks of intervention.

Neuropsychological testing, the standard outcome measure in cognitive intervention trials, will be used as a secondary outcome measure of cognitive function and activities of daily living (ADLs). For this outcome, we hypothesize that the CT, ET and CT + ET interventions will result in a significant improvement in episodic memory, sustained attention and ADLs relative to the AC condition.

Study Will Provide New Data

Due to the novelty of the study, we have proposed no specific hypotheses regarding the relative efficacy of CT, ET and CT + ET. If CT and ET are shown to improve cognitive functioning in this controlled trial of at-risk older adults, it will help advance research on cognitive decline and AD and contribute to effective intervention and treatment.

We are proposing a follow-up study to track subjects’ neuropsychological condition and conversion to AD. If ET and CT could delay AD onset by five years, disease prevalence would decrease an estimated 50 percent. This reduction could dramatically lower healthcare costs and improve quality of life for the growing population of people older than 65.

Stephen Rao, PhD, ABPP-CN, holds the Ralph and Luci Schey Chair and is Director of the Schey Center for Cognitive Neuroimaging at Cleveland Clinic. His specialty interests include functional brain imaging in healthy aging, mild cognitive impairment (a preclinical stage of Alzheimer’s disease), traumatic brain injury, prodromal Huntington’s disease and multiple sclerosis. Dr. Rao has received funding from the National Institutes of Health, Department of Defense and various foundations. He can be contacted at 216.444.1025 or raos2@ccf.org.

REFERENCES


Intraoperative MRI Suite Combines Advanced Imaging, Laser Therapy for Brain Tumors

By Michael A. Vogelbaum, MD, PhD

Intraoperative magnetic resonance imaging (MRI) technology has undergone several improvements since it was first used in the late 1990s but, until recently, obtaining near-real-time MR images during surgery posed drawbacks, particularly in terms of image quality and ability to use conventional surgical equipment and techniques. Cleveland Clinic has pioneered image guidance in neurosurgery, and continues this tradition with utilization of the IMRIS Neuro™ intraoperative suite, which addresses many of the challenges previously encountered. The suite was designed and constructed as a joint effort of our Imaging and Neurological institutes. This project, initiated with a Department of Energy grant awarded to the Imaging Institute, is an excellent example of a multidisciplinary approach to the application of technology for improved patient care.

Cleveland Clinic’s Brain Tumor and Neuro-Oncology Center is one of the first centers worldwide to pursue integration of the newest intraoperative MRI technology with its pioneering laser interstitial thermal therapy (AutoLITT™, Monteris Medical) capability to enhance brain tumor treatment.

In April 2010, the Brain Tumor and Neuro-Oncology Center performed its first procedures in the interventional MRI suite, and it is in the process of combining this high-field MRI guidance with the laser interstitial thermal therapy technology, monitored with real-time MRI thermometry. These technologies will allow for minimally invasive approaches to resecting brain tumors, and will provide a similar benefit to patients whose tumors cannot be resected safely. Ideal candidates for intraoperative MRI-guided surgery are patients with low-grade gliomas that do not enhance well, those with tumors thought to be nonresectable and suitable for LITT, and those with clinically difficult tumors that are adjacent to functional structures. Neurosurgeons in the Brain Tumor and Neuro-Oncology Center are trained to operate in the interventional MRI suite, and it is expected the suite will be used for 200 to 300 procedures annually.

Distinct Advantages

The interventional MRI suite is equipped with a movable 1.5 Tesla MR scanner with diffusion tensor imaging capabilities that provides high-resolution images during procedures. Previously, our center performed intraoperative MRI using the Odin N-20™ intraoperative system, a low-field, 0.15 T unit that could be extended upward from the sides of the operating table when imaging was required. While this system allowed us to use regular surgical equipment and to image...
patients without having to transport them away from the operating room, the low field strength produced relatively low-resolution images, and certain types of advanced MRI techniques could not be used. Furthermore, the low-field technology could not perform MR thermometry, which is a critical element for LITT therapy.

The new suite maintains safety by also eliminating the need to move the patient but, in contrast to our prior system, it allows us to obtain higher-quality MR images. The MR scanner is suspended from the ceiling and can be moved into the operating room for imaging, then out of the OR during the actual surgical procedure. This feature allows access to advanced imaging technology without restricting use of all our regular instruments, which are not typically MRI compatible.

The MRI unit incorporates an integrated data management and display system, along with a surgical information management system that provides timely and accurate depictions of changes in brain position and anatomy during surgery. Overall, the improvements offered with the intraoperative MRI suite can enhance surgical efficacy.

Additional Features

The intraoperative suite includes a patented overhead rail system that transports the MR scanner into the fully integrated operating room. When not needed for a neurosurgical procedure, the machine can be withdrawn to a separate MR room, where it can be used for traditional diagnostic purposes. The suite’s multifunctional operating room can serve as a conventional operating room when image guidance is not needed.

Laser ablation of tumors is an important new technology that Brain Tumor and Neuro-Oncology Center surgeons will use in the intraoperative MRI suite. The facility can provide intraoperative guidance for a range of other advanced neurosurgical procedures, including placement of deep brain stimulators and stereotactic EEG electrodes. As with the LITT procedure, it is anticipated that these interventions will be performed inside the bore of the MRI machine under direct MRI guidance. We in the Neurological Institute will gain the unique opportunity of real-time image feedback to guide instruments and stimulator devices to any point in the brain with the highest-level precision.

Michael A. Vogelbaum, MD, PhD, is Associate Director of the Brain Tumor and Neuro-Oncology Center at Cleveland Clinic. He is also a research scientist with special interest in benign and malignant brain and spinal cord tumors, Gamma Knife® radiosurgery, stereotactic surgery and the molecular biology of brain tumors.

SUGGESTED READING

Using High-Resolution MRI to Help Characterize Neurovascular Disease

By Ferdinand Hui, MD

Magnetic resonance imaging and magnetic resonance angiography are used extensively to evaluate such diverse disorders as stroke, neurocognitive decline, neoplasm, epilepsy and more. MRI and MRA help delineate disease states noninvasively and without radiation. By using a smaller field of view and contrast-enhanced MRI with saturation pulses to null blood, it is possible to obtain high-resolution magnetic resonance imaging that focuses on blood vessel walls. At Cleveland Clinic, we are making more frequent use of this advanced technique to investigate cerebrovascular diseases.

Homing in on Vascular Abnormalities

Stroke is the third leading cause of mortality in the United States, after heart disease and cancer. In both hemorrhagic and ischemic subtypes, imaging of the blood vessels helps to identify abnormalities that may be resulting in stroke.

Computed tomography is generally the first-line noninvasive imaging technique for patients with an acute change in mental status and/or neurological exam. CT is useful for determining the presence of new hemorrhage or an irreversible stroke, and for excluding the presence of a large tumor or the development of hydrocephalus. CT technology, however, exposes the patient to ionizing radiation. It is also relatively insensitive to a very early stroke, and may not provide the ability to image thin, abnormal blood vessel walls.

MRI and MRA utilize the ability of a magnet to change the magnetic spin of protons in the human body and track them within a volume. These magnetic spins allow for sophisticated imaging of the brain, affording highly sensitive images of acute and hyperacute strokes, the detection of blood and imaging of blood flow. Advanced techniques available with newer scanners allow teams to try to home in on the exact shape and distribution of vascular disease affecting a patient.

An Innovative Technique

High-resolution MRI may refer generally to MR images that focus on a small field with high spatial resolution. The technique described here refers specifically to imaging designed to assess the blood vessel wall:

A gadolinium-based contrast agent is infused into the patient, allowing for vessel wall enhancement. In order to eliminate enhancement of the flowing blood, a saturation pulse is placed at the neck to cancel the signal of the blood on its way to the brain. By creating a signal-nulled, “black blood” appearance, we can distinguish abnormal wall enhancement from the enhancement of the blood.

At Cleveland Clinic, we collaborate internally to identify cases that might benefit from further analysis with high-resolution MRI. This imaging modality may help physicians plan tailored treatment for several subtypes of stroke, including vasculitis, transient ischemic attacks associated with intracranial atherosclerosis and subacute ischemic strokes, as well as for aneurysm.

Vasculitides

This term describes a diverse group of diseases that result in inflammation of a blood vessel wall, which may reduce blood flow to the area of brain the blood vessel supplies. High-resolution MRI can be utilized to identify the most diseased segments, potentially helping to target blood vessels for biopsy. The technology can also help monitor response to treatment.
Intracranial Atherosclerosis

Intracranial atherosclerosis may account for 8 to 10 percent of ischemic strokes in North American populations, and the incidence appears to be higher in Asian, Hispanic, and black populations. Several European studies have shown a higher incidence in those populations than the numbers reported in U.S. studies. Detection of intracranial atherosclerosis and its characterization help physicians make decisions about treatment methodology.

Subacute Stroke

The presence of collaterals may help preserve brain at risk from ischemic stroke, in which blood reaches the brain indirectly once an occlusion of a major blood vessel has occurred. In these situations, understanding the nature of the blockage may help treating physicians decide how best to approach it and whether angioplasty and stenting may be necessary. Imaging of the thrombus may help to identify the morphology and characterize underlying atherostenotic disease.

Cerebral Aneurysm

Most angiographic techniques characterize the blood within an aneurysm sac. Increased thickness of an aneurysm wall may indicate areas difficult to surgically reconstruct, as thickened walls may make accurate microsurgical clip placement treacherous.

High-resolution MRI techniques have a place within the array of tools that medicine may employ to better stratify patients for treatment of intracranial vascular disease.

Blood vessel wall enhancement associated with an atherosclerotic plaque that caused a transient ischemic attack. Figure 1 shows a post-contrast high-resolution MRI of the left middle cerebral artery in the axial plane. Figure 2 shows the lesion in the orthogonal plane. Figure 3 is from the corresponding catheter angiogram.

Ferdinand Hui, MD, is an interventional neuroradiologist in Cleveland Clinic’s Cerebrovascular Center. His specialty interests include interventional and therapeutic neuroradiology, MR flow imaging, cerebrovascular disease and intracranial atherosclerosis. He can be reached at 216.445.9897 or huif@ccf.org.

SUGGESTED READING


Integrating Knowledge and Tools to Define the Epileptogenic Zone

By Richard C. Burgess, MD, PhD; Jorge Gonzalez-Martinez, MD, PhD; Stephen E. Jones, MD, PhD; and Dileep R. Nair, MD

For patients with medically refractory focal epilepsy (MRE), surgery has the potential to control seizures if the epileptogenic zone (EZ) can be accurately identified and completely removed. However, despite advanced surgical and neuroimaging techniques, the postsurgical success rate is less than 50 percent at five years for patients with non-lesional frontal lobe epilepsy. A major reason for the persistence of seizures following surgery is inadequate localization of the EZ. At Cleveland Clinic Epilepsy Center, neurologists, neurosurgeons, clinical neurophysiologists and neuroradiologists collaborate to selectively apply and actively investigate standard and novel diagnostic modalities, with the common goal of more accurately defining the EZ.

This multidisciplinary team, focused exclusively on epilepsy, reviews all cases and decides how to use diagnostic modalities to evaluate MRE surgical candidates, based on clinical history and test findings. Test results are carefully analyzed and interpreted to ensure that the EZ has been correctly identified and no brain abnormalities have been overlooked. Ultimately, the appropriate combination of technologies and the expertise of a dedicated group of specialists have proved crucial to optimizing patient outcomes.

Noninvasive Evaluation

EEG and Structural Imaging

Most surgical candidates first undergo noninvasive tests, including MR structural imaging and video-electroencephalogram (EEG) monitoring. MRI is considered the gold standard for structural imaging of focal epilepsy due to its superior soft-tissue contrast and multiplanar imaging capability. Structural MRI at 3 Tesla identifies focal abnormalities in more than half of patients with focal epilepsy. Identifiable lesions on MRI that may be epileptogenic foci include mesial temporal sclerosis, cortical development abnormalities, tumors, vascular malformations, stroke-damaged tissue and traumatic brain injuries.

Concordance between the structural lesion(s) and the ictal onset zone detected by EEG is associated with highly favorable surgical outcome. The highest predictor of surgical success is identification of a single, visible MRI lesion, but this occurs in less than 25 percent of patients. Nearly half of all epileptogenic foci do not exhibit an abnormality visible with conventional techniques, due perhaps to the small size of the lesion or inadequate contrast.

Functional Imaging

If the MRI scan is negative or shows multiple lesions, functional imaging tests such as SPECT or PET studies may be helpful in furthering the hypothesis of the location of the EZ. PET with fluorodeoxyglucose (FDG) measures glucose uptake, an effective assessment of brain metabolism; FDG-PET has a high sensitivity (84 percent) and specificity (86 percent) for temporal lobe epilepsy. SPECT pinpoints seizure “hot spots” with injection of a small amount of radioactive material into the patient’s bloodstream immediately after a seizure occurs. The radioactivity highlights increased vascular flow at the seizure site. With digital image processing, Subtraction Ictal SPECT co-registered to MRI (SISCOM) can show that a single area is responsible for the patient’s seizures, thus helping to better define a surgical strategy.

Magnetoencephalography

When the initial standard evaluations are unable to pinpoint the EZ, or when the results they yield are not entirely concordant with other structural and functional tests, another method for recording and localizing neural signals may clarify the origin of epileptic discharges. This novel alternative is magnetoencephalography (MEG).

The results of electroencephalography can be especially confusing when the patient has undergone a previous neurosurgical procedure, whereas MEG is not influenced by alterations or abnormalities of the skull. This
The magnetic equivalent of EEG, MEG is a direct electrophysiological measure of neural function that records the magnetic fields just outside the scalp on a millisecond-by-millisecond basis. MEG records mainly interictal spikes; the generator of these spikes is determined using mathematical models that must be carefully calculated. Because the MEG helmet that patients use has hundreds of sensors, and the magnetic field is not distorted by skull or fluid, this modality has greater localization accuracy than EEG and indicates more precisely where neural activity is originating.

MEG can localize activity during defined sensory or cognitive tasks, which makes it useful in presurgical mapping of eloquent cortex and as a research tool for fundamental study of the nervous system. The Elekta Neuromag® system at Cleveland Clinic simultaneously records MEG and up to 128 channels of EEG, allowing us to compare results in an epileptic patient. MEG can also be used to guide placement of invasive electrodes and to record concurrently with invasive evaluation.

Our hope is that in time, noninvasive diagnostic technologies such as MEG/EEG will replace some invasive evaluations that have higher sensitivity for localization of the EZ, but also increase the risk of morbidity.

Invasive Modalities

When noninvasive test findings are not concordant, invasive techniques may be required. This situation occurs in approximately 10 to 20 percent of patients. Indications for invasive evaluation include MRI-negative focal epilepsy, multiple structural lesions, suspected epileptic pathology extending beyond the structurally visible lesion, failed epilepsy surgery referred for possible reoperation and eloquent cortex adjacent to the suspected EZ.
Subdural Grids and Depth Electrodes

Subdural grids can be implanted over the cortical convexity, while depth electrodes are used primarily to study deep structures such as the medial temporal lobe. The placement of electrodes must be guided by a clear hypothesis about the potential location of the EZ, and the areas of cortex covered by the electrodes must be chosen to provide answers to the questions raised by the hypothesis. Otherwise, the evaluation may yield results that mislead or fail in localizing the EZ.

After surgical implantation of subdural grids and depth probes, continuous electrocorticographic (ECOG) monitoring is performed for passive recordings over a five- to 10-day period. The patient’s ictal and interictal epileptogenic zones are mapped, with particular attention to the time periods of ictal events; the electrode that demonstrates the earliest electrographic pattern is identified and defined at the ictal onset zone. Cortical stimulation with subdural grids also can be used to map various eloquent functions such as sensorimotor, language and visual regions.

Stereoelectroencephalography

Stereoelectroencephalography (SEEG) is another method of invasive monitoring, designed to more precisely localize areas of the brain responsible for seizure generation. SEEG entails implantation of small electrodes in brain areas defined on the basis of presurgical clinical and radiological information.

In March 2009, our Epilepsy Center launched the first SEEG program in the United States; this modality is commonly used at European epilepsy centers. Because SEEG enables placement of thin electrodes through smaller holes in the skull, it is less invasive than other invasive techniques. With eight to 16 contacts per electrode, it allows us to implant larger areas of the brain and to record both surface and depth. SEEG provides a three-dimensional neurological image of brain activity and illuminates the epileptic network, revealing how cortical regions are anatomically and functionally connected.

Investigating Brain Connectivity

During invasive evaluation, active recording of the cerebral cortex can be performed using cortico-cortical evoked potentials (CCEPs): single-pulse stimulation, with subdural electrodes, of brain electrical activity. CCEP is most useful for mapping eloquent cortex near the EZ and for studying functional as well as pathological connectivity in the epileptic cortex.

Brain connectivity is the new frontier of epilepsy research. When multiple epileptic foci exist, CCEP can identify connective areas of onset to determine the EZ. When there are no identifiable lesions, lack of connectivity in a certain location may indicate brain pathology; for example, white matter neurons may not be functioning and there may be an underlying lesion.

Among the promising future tools for assessing brain connectivity are noninvasive techniques such as MRI. In particular, the recently developed diffusion-weighted MRI is producing increasingly accurate models of white matter tracts inside the brain, which connect one region of cortex to another. What remains are methods to quantify, or “score,” these connections, then compare them against the gold standard scores from invasive evaluations. A successful, reliable comparison could validate a noninvasive technique, affording it considerable clinical influence by reducing or minimizing the requirement for invasive evaluation with its attendant morbidity.
For Surgical Success

Epilepsy surgery requires a multidisciplinary approach, the combined application of all available diagnostic modalities, astute data analysis and the drive to use modalities to discern the answers to difficult questions. As new technologies develop and research unveils the secrets of the epileptic brain, an increasing number of MRE patients may be able to realize their dream of seizure freedom in coming years.

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REFERENCES


Cleveland Clinic’s Multidisciplinary Care Model for Chronic Pain: Rethinking Our Approach to Chronic Disorders

By Jahangir Maleki, MD, PhD

Trained in the identification and treatment of acute medical illnesses, many clinicians intuitively subscribe to the maxim that “an effective treatment always follows a correct diagnosis.” Applying the same methodology when we encounter patients with chronic medical conditions, we compromise our ability to correctly identify and effectively manage the long-term consequences of these disorders.

Because the person with a chronic disorder suffers from both the dysfunctional body part and the slow effects of progressive, maladaptive changes to the individual organism as a whole, it is unlikely that treatment of the “part” can bring resolution to coexisting chronic problems that have gained their own momentum. This tendency to overlook ongoing changes to the entire organism is abetted by the trend toward subspecialization in medicine and fragmentation of healthcare.

The standard approach to diagnosing and treating chronic pain illustrates the shortcomings of our current healthcare model and its public health consequences. At Cleveland Clinic’s Neurological Center for Pain, a multidisciplinary team of pain specialists collaborates to treat chronic pain as a complex, multifaceted disease entity.

An Independent Illness

Approximately 40 million Americans are disabled by chronic pain. Myriad circumstances can initiate the pain cycle, help sustain it and/or prevent recovery. Thus, chronic pain may be the consequence of an incorrect and/or missed diagnosis, a suboptimal and incomplete recovery from an acute illness, or poor treatment. It can also ensue from cumulative traumas and maladaptive pathophysiological processes across the entire body, including the nervous system.

Irrespective of the cause, once chronic pain takes hold, it soon becomes an independent illness adding to individual suffering and disease burden. Not understanding this fact, we continue to expose patients to unnecessary tests and failed treatments.

Lacking Diagnostic Criteria

A need for more research—and for revision of our diagnostic nomenclature—directly reflects the limitations of our currently available diagnostic criteria, which fail to accurately define the complexities of chronic pain. The absence of consensus on this point is evident in the challenges we face in clinical practice.

Our diagnostic criteria do not differentiate among patients, particularly those who have failed previously acceptable treatment and/or those with complex medical histories. For example, diagnoses of inflammation affecting different tissues, such as myositis, discitis, arthritis and radiculitis, fill the medical records of patients with chronic lower back pain. Many of these patients have suffered for years and have repeatedly failed multiple interventions. The diagnosis of lower back pain is an oversimplification when we consider the vast individual differences we encounter in daily clinical practice. Patients differ significantly in the history and duration of their pain and in the type/

A 35-year-old female presented with pain level of 10/10 and a Pain Disability Index (PDI) score of 50/70. She was also profoundly depressed. Her pain, involving lower back and left lower extremity, had been present for about 15 years. She had been diagnosed with lumbar spondylosis and had tried multiple medications, including 12 spinal injections. Her condition was complicated by a diagnosis of multiple sclerosis over the past 12 years (visible in scan at left), which had been treated with numerous courses of IV steroids and immunomodulatory medications. Upon completion of Cleveland Clinic’s Chronic Pain Rehabilitation Program, she was discharged with almost complete resolution of her symptoms. Her activities were unrestricted, as her PDI had improved to 4/70 and her pain to 1/10, and the depression was completely resolved.
outcome of treatments. Lower back pain is associated with varied outcomes in the presence of comorbid conditions such as rheumatoid arthritis with multiple joint deformities, Crohn’s disease, spondylolisthesis and failed back surgeries.

As seen in failed back syndrome, the diagnostic criteria are less clear in light of the increased incidence of long-term opiate use and interventional pain procedures performed on chronic pain patients—and the failed response. The very term, “chronic pain,” can be viewed as a rebuke, reminding us of its unremitting nature and the limits of our understanding of the neurobiology of pain disorders.

**Individualized Care**

At Cleveland Clinic’s Neurological Center for Pain, we commonly see patients whose chronic pain is associated with multiple sclerosis, fibromyalgia, arachnoiditis, Chiari malformation, peripheral neuropathy and general spine/neck injuries, among other disorders. In each case, we initiate treatment with a comprehensive evaluation. This assessment comprises general aspects of organ system disorders commonly encountered in these patients as well as individual variations that make the expression of chronic pain unique in each person.

The initial assessment includes physical, neurological and psychological components to identify “pain generators” and comorbid medical conditions that sustain the pain. Additionally, we seek to identify any pre- or coexisting medical illnesses that may interfere with successful treatment and rehabilitation (see Figure 1).

Under our disease-based care model, findings from the assessment dictate the composition of a multidisciplinary team of pain specialists and the development of an individualized treatment plan. Further diagnostic workups may be required to identify and treat any undetected causes of pain. To facilitate the rehabilitation process, we may need to address the pain with pharmacotherapy and/or with interventional pain management techniques such as intravenous, regional and spinal injections and/or infusions before patients are able to participate in physical and psychological therapies. Our treatment plan is geared toward long-term remission, not short-term relief.

Specific treatment protocols range from a simple medication adjustment to a combination of comprehensive medical, rehabilitative and behavioral health services. Some patients require referral to a specialized, three- to four-week program of intensive multidisciplinary rehabilitation.

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Our ultimate goal is to achieve a remission in pain and empower our patients to manage this chronic disorder so they can again participate in activities they enjoy and significantly improve their quality of life.

Jahangir Maleki, MD, PhD, is a pain management specialist with training in neurology, psychiatry and interventional pain management. His specialty interests include diagnosis and management of chronic pain disorders, and central and peripheral mechanisms of pain processing. He is board certified in neurology, clinical neurophysiology and pain medicine. He can be reached at 216.445.8814 or malekij@ccf.org.
Deep Brain Stimulation of the Ventral Capsular/Ventral Striatal Area for Modulation of the Affective Component of Central Thalamic Pain Syndrome

By Andre G. Machado, MD, PhD

Central pain syndrome can arise as a complication of central nervous system lesions involving the somatosensory pathways. These syndromes can be secondary to any type of injury, including trauma or stroke, and can be associated with injury along any point of somatosensory transmission in the central nervous system, including the spinal cord. Central pain syndrome may occur after thalamic strokes or thalamic lesions, with anesthesia dolorosa, or painful numbness, of the opposite side of the body. Most neuromodulatory approaches thus far have attempted to modulate somatosensory pathways or diminish abnormal pain transmission. The clinical goal is usually to reduce the intensity of pain by 50 percent, as measured by a visual analog scale of pain.

At Cleveland Clinic, a new approach for managing severe and refractory central pain has been proposed, targeting the ventral capsular/ventral striatal area with deep brain stimulation (DBS). The goal is to modulate the affective component of this chronic pain disorder and, consequently, to reduce pain-related disability.

A Clinical Challenge

Debilitating and often difficult to treat, thalamic pain syndrome occurs after a stroke or other injury to the thalamic region. The pain, which can be limited to one limb or affect an entire half of the body, may include constant dull aches and severe, unrelenting burning. Complicating diagnosis and treatment, symptoms may not appear until weeks or months after the initial injury. The pain is frequently unremitting and causes significant impairment and loss of quality of life.

The first line of treatment is pharmacotherapy. Tricyclic antidepressants and anti-seizure medications may be attempted, with varying degrees of success. Typically, patients with refractory pain receive progressively stronger narcotic analgesics, which often provide relatively short-term benefits.

Surgical treatments are sometimes attempted in patients with disabling pain that has been refractory to management with various types of medication. However, the most effective surgical option for central pain syndrome remains to be found. In the past, DBS of the periventricular gray area, sensory thalamus or motor cortex showed some promise in a fraction of patients with medically refractory thalamic pain syndrome. However, results proved to be less consistent than those observed for DBS for movement disorders or neuromodulatory approaches for peripheral neuropathic syndromes.

A Novel Neuromodular Approach

With a $1.5 million grant from the National Institutes of Health, we are embarking on a research study that departs from the conventional approach and outcome goals for managing thalamic pain syndrome and builds upon our contemporary understanding of chronic pain physiopathology.

Chronic pain is not a purely somatosensory experience; it also has significant affective and cognitive spheres, as proposed by Melzack’s “neuromatrix.” To a large extent, neurostimulation approaches aimed at modulating the somatosensory sphere of chronic central pain have failed. In this research study, we plan to evaluate if DBS of the ventral anterior limb of the internal capsule and the adjacent ventral striatum (VC/VS) will modulate the affective component of thalamic pain syndrome and, consequently, reduce pain-related disability.

The groundwork for this approach was laid by a multicenter collaborative study that included Cleveland Clinic, which has investigated stimulation of the VC/VS in patients with treatment-resistant depression and those with refractory, disabling obsessive-compulsive disorder (OCD). Significant improvement in symptoms has been observed in both groups of patients, and the method has been found to be safe and reproducible.

Our pilot clinical study will determine the safety and efficacy of DBS of the VC/VS in patients with intractable thalamic pain syndrome. The research will mark the first time this disorder will be treated with DBS of the VC/VS, a region densely populated with fibers related to neural networks that are linked to control of behavior and emotion.
Methodology

Enrollment in this phase will be limited to 10 subjects who have experienced chronic, disabling pain for longer than six months, which is refractory to pharmacological management. Patients will undergo bilateral DBS surgery, during which electrodes will be implanted on either side of the brain to deliver stimulation to the targeted neural networks. Patients will be randomized to either an active treatment group or a sham stimulation group and then crossed over. Those undergoing active treatment will receive stimulation settings that have been titrated and optimized for clinical efficacy. Patients in the sham stimulation group will receive no stimulation via the DBS systems. Patients and investigators collecting outcome measures will be blinded.

Study subjects will undergo baseline and post-DBS double-blinded evaluations for six months, followed by chronic open-label stimulation. The neural circuits affected by central pain syndrome and the effects of DBS on these networks will be studied regularly with functional imaging techniques.

We have departed from the Visual Analog Scale as the primary outcome measure for chronic pain neuromodulatory studies. In this study, we have selected the Pain Disability Index as the primary outcome measure. The intent is to focus not only on how much DBS can alleviate pain intensity—which can be difficult to measure in patients with chronic pain—but, rather, to evaluate primarily how much DBS of the VC/VS can alleviate pain-related disability. We anticipate that patients with improved pain-related disability will also enjoy better quality of life after VC/VS deep brain stimulation surgery.

Andre G. Machado, MD, PhD, is the Director of the Center for Neurological Restoration at Cleveland Clinic. His specialty interests include deep brain stimulation for Parkinson’s disease, essential tremor, dystonia and other movement disorders as well as surgical treatments for chronic pain syndromes. His research interests include deep brain stimulation for the treatment of refractory depression and OCD as well as emerging deep brain stimulation therapies, such as for central pain and stroke rehabilitation. His laboratory studies the effects of deep cerebellar stimulation on the recovery of motor function following stroke translational models. He can be contacted at 216.445.4270 or machada@ccf.org.

SUGGESTED READING


Forced Exercise Holds Promise as Novel Intervention for Parkinson’s, Other Neurodegenerative Diseases

By Jay L. Alberts, PhD

Although studies in animal models of Parkinson's disease (PD) have shown that exercise improves motor function and has neuroprotective benefits, results of clinical research investigating the effects of exercise in human PD patients have been less promising. Specific exercise regimens have been associated with a few specific improvements in patients with PD, such as increased strength following weight lifting or increased walking speed after treadmill training. However, the exercise protocols studied failed to produce any type of global motor improvements using accepted clinical rating tools such as the Unified Parkinson’s Disease Rating Scale (UPDRS) or improvements in parts of the body that were not being exercised.

Personal coincidental observations I made on two separate occasions of remarkable symptomatic improvements in PD patients sharing a tandem bicycle with me, a trained cyclist, motivated me to look further to try to understand the discrepancy between the promising results of the animal research and the marginally effective human studies. This interest has led to a clinical study program that we hope will establish exercise as a novel intervention for improving motor function and altering brain function in patients with PD. If successful, the research is exciting, not only because a treatment approach based on exercise will convert patients from a passive role in their disease management to active participation, but also because discovering a treatment that affects brain function might positively alter (i.e., slow) the natural course of PD and, possibly, other neurological diseases.

Exercise Intensity and Motor Function Improvement

Closer consideration of the research conducted in rodent models of PD revealed that these exercise regimens involved a “forced exercise” paradigm under which the animals were placed on a treadmill and exposed to an external stimulus as needed to assure they maintained a set pace, which was faster than their naturally preferred walking speed. In contrast, exercise intensity for participants in previous clinical studies was under their individual or voluntary control. I postulated that the tandem bicycle riding might be a form of forced exercise that could be responsible for the patient-noted improvements in motor function while cycling. Animal research showing a direct correlation between increasing rate of exercise and the level of global motor function improvement was also consistent with the idea that differences in exercise rate might explain the inconsistency in outcomes between the animal and clinical research.

In 2007, we initiated a proof-of-concept study to investigate the hypothesis that PD patients might derive motor function benefits from physical exercise, if given the opportunity to exercise at rates higher than they could normally achieve. The results were recently published in a leading rehabilitation journal. The study randomized 10 PD patients into voluntary and forced exercise groups, the former riding a stationary single bicycle at a voluntary rate and the other riding a stationary tandem bicycle with a trained cyclist. The tandem group was assisted at pedaling between 80 and 90 revolutions per minute, while the voluntary group pedaled at its preferred rate.

Patients in both groups completed one-hour exercise sessions, three days a week for eight weeks at similar aerobic intensities. Assessments were made at baseline, at the end of the exercise program and four weeks after its completion, and included a fitness evaluation of maximal oxygen uptake (VO₂ max) and motor function evaluations using clinical ratings (the UPDRS Part III motor score) and a biomechanical assessment of manual dexterity. The latter was included as a specific measure of motor function in the non-exercised upper extremities to explore the concept that forced exercise produced global effects and resulted in positive changes in central motor control processes.
Imaging Shows Increased Brain Activation

After eight weeks of exercise, patients in both groups achieved significant improvements in aerobic fitness. However, motor function benefits were observed only in the forced exercise group. After eight weeks of the forced exercise program, patients exhibited a 35 percent improvement over baseline UPDRS III scores, which was statistically significant. While their scores worsened four weeks later, they still showed an improvement over baseline that approached statistical significance.

More strikingly, the forced exercise group showed a significant improvement in manual dexterity that was maintained at the follow-up examination four weeks after cessation of the exercise program. The latter changes included improved coupling of grasping forces, interlimb coordination and rate of force production. There were no significant changes from baseline UPDRS III or manual dexterity scores in the voluntary exercise group immediately after exercise ceased or at the follow-up visit.

Encouraged by these results that indicate the forced exercise program may be having a disease-modifying impact and not just a symptomatic effect, we undertook a short-term follow-up study to examine changes in brain function using functional magnetic resonance imaging (fMRI). Conducted in collaboration with Micheal Phillips, MD, Department of Neurosciences, and Mark Lowe, PhD, Department of Diagnostic Radiology, the study had a crossover design in which PD patients underwent imaging on three separate occasions: 1) three to four hours after completing a forced exercise session, 2) three to four hours after taking their anti-PD medication and 3) when there was no exposure to exercise or medication. The order in which the different test situations were conducted was randomized across subjects. The fMRI scans showed that compared with the control visit, exercise and medication produced similar neural responses in terms of increasing activation levels in both the cortical and subcortical areas of the brain.

New Data Forthcoming

We have expanded our research into a larger clinical trial being conducted at the Cleveland Clinic main campus and at our Lou Ruvo Center for Brain Health in Las Vegas. Our goal is to recruit 60 patients who will be randomized to a no-exercise control group or to an eight-week program of voluntary or forced exercise, with a follow-up assessment again after four weeks. Endpoints include the same clinical and biomechanical measurements assessed in our pilot study, along with additional biomechanical measurements of lower extremity function and postural stability. This trial also includes an imaging component that will provide the first data on possible long-term effects of forced or voluntary exercise on brain function. Patients in the forced exercise group are using a motorized stationary single bicycle that would be more practical for adaptation to clinical or home use.

The mechanism(s) by which forced exercise produces the neural and motor changes we have observed are unknown. However, there is evidence that peripheral nerve stimulation increases excitability in the motor cortex, and animal research indicates that forced exercise is associated with increased brain levels of dopamine and/or neurotrophic factors (GDNF or BDNF). If forced exercise induces these neurochemical changes, it may have exciting potential to slow disease progression and delay the need for medical therapy in patients diagnosed with PD. Looking ahead and considering that these neurotrophic factors have established importance in the acquisition of motor skills, the opportunity to positively alter their levels by forced exercise has us thinking about future research investigating this intervention in Alzheimer’s disease, rehabilitation for stroke and other neurodegenerative disorders.

Jay L. Alberts, PhD, is a researcher in the Department of Biomedical Engineering at Cleveland Clinic Lerner Research Institute and a Staff Member in the Center for Neurological Restoration. His specialty interests include the effects of deep brain stimulation on motor function of Parkinson’s disease patients and the effects of unilateral DBS on bilateral motor function. He can be contacted at 216.445.3222 or albertsj@ccf.org.

REFERENCE

A Team Approach to Diagnosing and Treating Peripheral Nerve Disorders

By Steven Shook, MD; Michael Steinmetz, MD; and Milind Deogaonkar, MD

Peripheral nerve disorders are very common, causing pain and loss of motor and sensory function, and they present the clinician with both diagnostic and treatment challenges. Some cases—particularly neuropathies resulting from trauma, entrapment or nerve tumors—are surgically treatable, with excellent outcomes. The pillars of successful outcome are proper and timely diagnosis, accurate localization and timely intervention.

Symptoms and Diagnosis

Surgically treatable disorders affecting a spinal nerve root, plexus or individual nerve trunk may be due to an external insult, such as traumatic injury, or internal entrapment. Nerve lesions, such as peripheral nerve sheath tumors, intraneural ganglion cysts and neuromas, are also potentially amenable to surgery. Typical symptoms in all cases include loss of associated motor and sensory function and pain. Neuropathic pain is usually described by the patient as numbness, tingling (e.g., “pins and needles”), burning or electrical in quality.

Determining whether a surgical approach to neuropathy is appropriate requires a comprehensive evaluation, including clinical history and neurological examination. In order to determine whether the nerve is structurally and functionally continuous, additional testing may be needed, including electromyography (EMG), neuromuscular ultrasound and magnetic resonance imaging (MRI) of the nerve tissue (also known as MR neurography). The underlying pathology and severity of the injury, as identified by this evaluation, determine prognosis and appropriate treatment.

Varied Treatment Options

Treatment planning begins with a multidisciplinary team discussion regarding the likely nerve injury type and prognosis:

- When damage is limited to the insulating covering of the nerve fiber—known as the myelin sheath—and the nerve axons and supporting connective tissue are intact, patients usually recover spontaneously within weeks and may not require surgical intervention.

Positioning Technology for Neuropathic Pain Relief

A peripheral nerve stimulator is an option for patients with chronic, localized neuropathic or soft-tissue (nociceptive) pain. Cleveland Clinic neurosurgeon Milind Deogaonkar, MD, who specializes in management of chronic pain and surgical treatment of peripheral nerve disorders, has developed a minimally invasive procedure for placing the stimulator that involves positioning the leads below the painful region, rather than directly on the nerve.

For ulnar nerve neuropathies, for example, the leads are placed just below the skin of the forearm instead of on the nerve. With subcutaneous placement, impulses from the stimulator inhibit weaker pain impulses, thus blocking the pain in muscles in that region.

Dr. Deogaonkar has applied this technique successfully for inguinal pain, neuralgia in limbs, back pain, atypical face pain and trigeminal neuralgia, and post-treatment nerve injury.

Patients with trigeminal nerve injury secondary to multiple surgical procedures for trigeminal neuralgia have no other option. With the electrodes placed below the skin of the face, these individuals are virtually pain free. To date, 48 of 53 patients who have undergone a stimulator implant report significant (average 70 percent) pain relief.

Lateral skull X-ray showing stimulator electrodes across the supra-orbital, infra-orbital, mandibular and occipital nerves.
• Recovery is delayed and often incomplete when the nerve axons are damaged (known as axonotmesis). In these cases, recovery is dependent upon the degree of “axon loss” and condition of the supporting connective tissues surrounding the individual nerve fibers (endoneurium), nerve fascicles (perineurium) and nerve trunk (epineurium).

• Complete transection of the nerve trunk (known as neurotmesis) is the most serious injury type, which typically will not recover without surgical intervention.

After an axon loss injury, regenerating nerve fibers extend toward their target at a rate of 1 mm a day. Recovery of motor function requires nerve fibers to reconnect with muscle fibers before atrophy and fibrosis occur. For this reason, early recognition of axon loss is critical to ensuring the best possible outcome.

Early exploratory surgery is usually recommended for patients with evidence of nerve transection. Conversely, axon loss injuries “in continuity” (i.e., without nerve transection)—which may occur due to compression or stretching of a nerve trunk—may be followed by the team for an observation period of three to six months to determine the degree of spontaneous recovery prior to making a decision regarding surgery.

For patients with no clinical or EMG evidence of motor function recovery, exploratory internal or external neurolysis with intraoperative nerve action potentials (NAPs) may be required. In the operating room, the neurosurgeon can evaluate a nerve segment across the point of injury. In some patients, NAPs are intact and neurolysis to free the nerve from adhesions is sufficient to restore function and relieve pain. If NAPs are absent, further surgical intervention may be required.

In some cases where injury is very recent and a simple, clean transaction is identified, directly reattaching the ends of the nerve (“end-to-end repair”) is adequate. When a gap is present between the ends to be reattached, due either to the length of the injured segment or retraction of the stumps after transection, a graft must be placed between the damaged ends. Regenerating nerve fibers grow from the proximal nerve stump, through the graft, through the distal nerve segment into the target muscles, potentially restoring function. In other cases, neurotization, in which nerve fibers are redirected from a healthy nerve into the distal stump of a damaged nerve, may be the best option. For example, a healthy intercostal nerve or its proximal stump is used to reinnervate the target motor territory.

Delay Can Be Costly

Timing plays a major role in the success of treatment for these disorders. Ultrasound and MR neurography can determine whether a nerve is “in continuity” immediately after symptom onset. EMG can detect and quantify axon loss as early as three weeks after an injury.

The degree of functional recovery always depends on the severity of the injury and the elapsed time between symptom onset and treatment. Delay in evaluation can seriously limit treatment options.

Successful Nerve Tumor Excision

By Milind Deogaonkar, MD

A 65-year-old female presented to us with a palpable mass in the medial aspect of her lower leg. It was located approximately 10 cm above the medial malleolus. She had noticed it three years prior, when it was much smaller and softer. Initially, she had severe pain and spasticity in her lower leg due to the mass, which grew gradually.

She underwent neuromuscular ultrasound, which showed a focal enlargement of the right tibial nerve (approximately 8 to 18 cm proximal to the medial malleolus), maximal at 10 cm proximal to the malleolus. It appeared heterogeneous, spherical and contained within the epineurium, with moderate posterior acoustic shadowing. Minimal Doppler signal was present within the lesion. These findings are most consistent with a neurona, perhaps a neurofibroma. Electromyography showed a right posterior tibial mononeuropathy.

Diagnosed with a right posterior tibial nerve tumor, the patient underwent surgery to excise it. Ultrasound defined the margins of the growth. The nerve was located distal and proximal to the tumor and the posterior tibial vessels were located over the anterior aspect of the tumor. Through a linear incision, the tumor was exposed (Figure 1).

After careful micro-dissection, the tumor was dissected away from the nerve (Figure 2) and completely excised, without damage to the nerve. The patient had a full symptomatic recovery with no new deficits. The pathological diagnosis was schwannoma.

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**CASE STUDY**

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Toward a Better Understanding of the Underlying Biology of Tinnitus

Studies Focus on Noise-Induced Neuronal Hyperactivity in Brain’s Auditory Centers

By James Kaltenbach, PhD

Tinnitus is the perception of an ongoing sound that has no external physical stimulus. Estimates of the incidence of tinnitus in the general population range from 4 to 16 percent, with approximately 0.5 to 4 percent experiencing tinnitus in a severe, disabling form. Excessive exposure to noise is by far the single most commonly cited cause of tinnitus. The pervasive and often unavoidable nature of loud noise in modern societies means that tinnitus is likely to be a significant clinical problem for a long time to come, and underscores the need for an understanding of its underlying biology. At present, treatments for tinnitus are mostly palliative in nature, attempting to improve quality of life without necessarily reducing or reversing tinnitus symptoms.

Effects of Intense Sound Exposure

We have been investigating changes that occur in the brains of animals treated with tinnitus-inducing agents, such as intense noise and cisplatin. We found that when rodents are exposed to intense sound for prolonged periods, neurons in the auditory centers of the brain become hyperactive. Neurons are induced into a state of elevated resting activity that normally occurs only when the cells are responding to external sound (Figure 1).

The structures we have focused on are located in the lower auditory brain stem and include the dorsal cochlear nucleus (DCN) and inferior colliculus. The “hyperactivity” is now widely regarded as a neural correlate of tinnitus because the same conditions of loud sound that induce hyperactivity also cause tinnitus in human subjects, and behavioral studies have shown that similar percepts are experienced by animals. Moreover, imaging studies have shown that the auditory centers of the brain are often hyperactive in patients with tinnitus. Thus, an understanding of the mechanisms underlying hyperactivity induced by loud noise (Figure 2) is helping to pave the way for translational research aiming to protect against or even reverse the condition of tinnitus-producing hyperactivity.

Areas of Inquiry

**NMDA Receptors**

Several targets are now under investigation in our laboratory. One of these, the NMDA receptor, is of interest because of its well-known role in the mediation of excitotoxic injury and neural plasticity. Excitotoxic injury to neurons occurs when certain neural pathways are overstimulated. Too much stimulation can cause excess release of glutamate (an excitatory neurotransmitter), which can trigger excess influx of calcium into cells. The excess calcium is toxic to neurons and causes them to degenerate. This mechanism may underlie the degeneration of inhibitory synapses that accompanies the emergence of hyperactivity in the DCN after noise exposure. We have found that the degree of noise-induced hyperactivity in the DCN can be greatly reduced by treating animals with an NMDA receptor blocker before they are sound exposed.

NMDA receptors are also key players in neural plasticity, a phenomenon that can lead to increases in the levels of neural activity. Our group is currently investigating the potential of the NMDA receptor blocker neramexane to eliminate tinnitus-related activity in the DCN after it has been induced by noise exposure.

**Acetylcholine**

We also are investigating the receptor for the neuromodulator acetylcholine. This agent is released by descending pathways of the auditory system, and is another plastic mechanism the brain uses to adjust the level of neuronal excitability. Following noise-induced hearing loss, there is an increase in the sensitivity of the DCN to acetylcholine. This increase is suspected of contributing to the induction of tinnitus-related hyperactivity. Because this form of neural plasticity is often reversible, it is likely to be the key to developing effective tinnitus therapies.

Our tinnitus clinic is investigating a form of sound therapy designed to stimulate the ear over the range of hearing loss, thereby removing the trigger of neuromodulation changes leading to tinnitus. We are also investigating new approaches to activating pathways that will turn down the gain on the acetylcholine-releasing system.

**Cisplatin Chemoprotectants**

Cisplatin, known for its wide application in cancer chemotherapy, also induces hearing loss and tinnitus because of its toxicity to cochlear outer hair cells. Our research has shown that cisplatin-induced damage to cochlear outer hair cells can be largely avoided if cisplatin is
administered in combination with other agents that protect the outer hair cells from injury. Two candidates that appear to be highly promising chemoprotectants are sodium thiosulphate (STS) and amifostine (WR2721). Future studies are planned to determine whether the protective effects of these agents can be achieved without loss of the anti-tumor effect of cisplatin.

James Kaltenbach, PhD, is Director of Otology Research in Cleveland Clinic’s Head & Neck Institute and a researcher in the Department of Neurosciences of Lerner Research Institute. His research interests include tinnitus, hyperacusis, hearing loss and ototoxicity. He can be reached at 216.444.5171 or kaltenj@ccf.org.
The Case for Early Metabolic, Genetic Screening in Children with Epilepsy

By Sumit Parikh, MD, and Prakash Kotagal, MD

Neurogenetic and metabolic screening in patients with idiopathic mental retardation and epilepsy, although becoming more common, is not as common or as systematic as it should be given the significant benefits to be derived from such analyses. A comprehensive screening protocol can clarify disease etiology, sharpen prognosis, refine therapies toward greater efficacies and allow for the design of more effective preventive strategies. Identifying the gene or genes involved can initiate family genetic counseling and education of patient and family regarding prognosis and signs of disease progression. In addition, genetic identification can provide the foundation for effective preventive efforts.

Studies suggest that 5 percent of children with epilepsy and idiopathic developmental delay may have some form of metabolic disease.

Unique Study Shapes Screening Protocols

Cleveland Clinic Center for Pediatric Neurology and Neurosurgery established a comprehensive screening program more than five years ago. As part of this program, we endeavored to define the clinical benefits of metabolic testing by reviewing the records of 429 children admitted to the Pediatric Epilepsy Monitoring Unit in 2005. Electroencephalogram results were noted. The presence or absence of developmental delay also was noted, owing to its association with metabolic disease.

We found that 28 percent of our patients demonstrated mitochondrial dysfunction (95 percent confidence interval, 22-43 percent). This percentage is significantly larger than the generally accepted ratio of > 5 percent, and may be explained in part by a selection bias associated with Cleveland Clinic’s status as a tertiary referral center. Despite this caveat, the presence of metabolic abnormalities in such a significant number of patients should accentuate the need for a diagnostic protocol that includes a routine approach to metabolic testing.

Genes May Underlie Treatable Metabolic Conditions

A host of potentially treatable metabolic disorders exists—many diagnosable only by spinal fluid analysis. Many of these conditions were unknown until the 1980s and 1990s, and their true incidence and range of phenotype are still being discovered. Because these disorders are treatable with diet change and/or vitamins and cofactors, it is crucial not to overlook them. These genetic metabolic disorders should always be considered in a neonate with unexplained refractory epilepsy. Vitamin-responsive diseases, which frequently present with neonatal epilepsy, are treatable. They include pyridoxine- and folinic acid-responsive seizures, glucose transporter defect, biotinidase deficiency, serine deficiency and creatine synthesis disorders. Mitochondrial disorders and neuronal ceroid lipofuscinoses present in late infancy and childhood. Unfortunately, we do not yet have therapies specific to the lipofuscinoses.

The value of genetic testing, and also of metabolic testing, is that it provides the patient’s family with a prognosis, allows preventive therapeutic strategies to be devised and helps the family make decisions about future procreation. Our experience is that parents are comforted by the knowledge we obtain from the testing.

Case Illustrates Benefits

A recently published case study demonstrates the value of metabolic testing. A 9-month-old girl was referred to Cleveland Clinic for surgery for refractory status of epilepticus suggestive of right hemispheric focus. Her MRI was unremarkable. Metabolic evaluation conducted according to the institution’s new protocol found a spinal fluid peak characteristic...
of folinic acid-responsive epilepsy. (Subsequent tests identified a mutation in the ALDH7A1 gene.) Folinic acid and pyridoxal 5'-phosphate supplementation therapy was initiated. Surgery was avoided and the child remained seizure free to her last follow-up two years postdiagnosis.

We believe that metabolic abnormalities are a significant clinical finding, especially in patients with unexplained developmental delays and refractory epilepsy. Mitochondrial metabolism disorders deserve to be high on a differential diagnosis. A number of these disorders can be readily identified and treated.

Our continuing work with our in-house metabolic specialists and close rapport with contracted testing facilities have allowed us to refine our initial protocols and identify tests most likely to be productive. As science and technology advance, we anticipate that many more metabolic disorders will be associated with specific genetic abnormalities, allowing for the design of therapies that will target these disorders with greater accuracy and efficacy.

Sumit Parikh, MD, is a neurometabolic and neurogenetic Staff Clinician in Cleveland Clinic’s Center for Pediatric Neurology and Neurosurgery. His specialty interests include the genetic diagnosis and treatment of patients with mitochondrial cytopathies, inborn errors of metabolism, cognitive and developmental regression, autism and developmental delay. He can be contacted at 216.444.1994 or parikhs@ccf.org.

Prakash Kotagal, MD, is Head of the Pediatric Epilepsy Section in Cleveland Clinic’s Epilepsy Center. His specialty interests include pediatric epilepsy, epilepsy surgery, vagus nerve stimulation, seizure symptomatology, and the relationship between sleep and epilepsy. He can be contacted at 216.444.9083 or kotagap@ccf.org.

REFERENCES


Rehabilitation of America’s First Face Transplant Patient

By Vernon W.H. Lin, MD, PhD

In December 2008, an interdisciplinary team of Cleveland Clinic rehabilitation specialists comprising a physiatrist, occupational therapist (OT), physical therapist (PT) and speech-language pathologist began treating a uniquely challenging patient: America’s first face transplant recipient. The patient, a 45-year-old woman with severe mid-face trauma due to a gunshot wound four years earlier, would require a rehabilitation regimen like no other.

During the 22-hour transplant procedure, a team of eight Cleveland Clinic surgeons replaced 80 percent of the patient’s face with a tailored composite tissue allograft; only the upper eyelids, forehead, lower lip and chin were not replaced. This surgery—the largest and most complex face transplant among the 10 performed worldwide to date—integrated different functional components, such as nose and lower eyelids, as well as different tissue types, including skin, muscles, bony structures, arteries, veins and nerves.

Clinical Evaluation

In conducting a clinical assessment of the patient, clinicians took into account the unique nature of the treatment and the patient’s condition. For example, the psychosocial history included perceived body-image adaptation and anticipated comfort with donated facial transplant. The physical examination emphasized the motor and sensory function of the facial nerve, facial expression, facial symmetry, oral function and olfaction.

Two scales have been developed for evaluating function specifically in facial rehabilitation: the Facial Grading Scale and the Facial Disability Index. Both will need further evaluation and testing before they can be adopted as standard tools for patients undergoing facial transplantation.

Continuum of Care

The interventions commonly used in facial neuromuscular rehabilitation include patient education, facial muscle therapy, speech and swallowing training, olfactory sensation and smell training, activities of daily living (ADLs), vision training and psychosocial function. Of these, ongoing patient education is the factor most important for success.

Intensive Care Unit

At Cleveland Clinic, physical therapy and occupational therapy evaluations for the patient were initiated in the Intensive Care Unit seven days postsurgery. The patient required complete assistance with mobility and ADLs. At first, PT and OT provided concurrent therapy due to the patient’s physical state and need to undergo medical tests and procedures. To allow the patient time to heal, facial movement exercises were not attempted.

Nursing Floor

When the patient transferred to the regular nursing floor 22 days postoperative, PT and OT set new goals to increase activity tolerance with mobility, independence with ADLs and smell recognition, while adhering to postoperative surgery precautions. PT worked with the patient on strength, mobility and endurance.

Progression of the facial transplant process. Figure 1: Facial deformity before face transplantation indicates multiple reconstructions of soft tissue and bones with plates. Figure 2: Composite facial allograft, procured from the donor, contains soft tissues, bones and muscles as well as functional units of nose, upper lip and lower eyelids. Figure 3: Facial allograft inset for reconstruction of the severe facial defect presented in Figure 1.
The speech-language pathologist assessed baseline speech function and began facial animation and tissue stimulation one to two times a day, five days a week, taking care not to be overly aggressive with oral-motor exercises and digital stimulation, given the significant edema of the donor tissue and the ongoing healing of the suture lines. The patient was given 11 basic exercises to perform independently and with her nurses two to three times daily. They included jaw range-of-motion movements, labial retraction and pursing, scrubbing of the nose and whole face, eyebrow raising and eyelid lowering, along with production of exaggerated labial speech and non-speech movements (such as “wow” and “woo”).

Because the patient was legally blind, all written material had to appear in large letters for her to read, and mirror feedback or visual cues for motor movements were challenging. Tactile cues were imperative. The patient was encouraged to touch the therapist’s face as movements were demonstrated prior to her own attempt to duplicate. OT provided her with a helpful reading magnifier. Collaboratively, OT and speech-language pathology began integrating functional facial gestures, including kissing, winking, blinking and blowing.

At four weeks, dentistry fitted the patient with an initial palatal obturator that did not include teeth, which enabled her to ingest a liquid diet and begin oral phase swallowing therapy. After many adjustments to close off the palatal defect and add teeth to the plate, the patient was allowed to eat soft solid foods.

**Postdischarge from Acute Care**

As care shifted to acute rehabilitation, treatment sessions occurred three to five times a week, with more aggressive digital stimulation to further facilitate facial sensation and motor movement. Facial expression exercises were initiated, among them exaggerated smiling, frowning, surprise, fear, pain and anger.

Upon the patient’s discharge from acute care, OT worked with her on community reintegration activities, accompanying her as she performed functional mobility in the community for the first time since her surgery. At discharge from OT services, the patient was independent with ADLs and modified independent with instrumental ADLs. PT services had been discharged upon the patient’s discharge from the nursing floor, when she demonstrated independence with mobility, strength and her individualized exercise program.

**Community Re-Entry/Home**

After 18 weeks of acute care and acute rehabilitation-level speech therapy at Cleveland Clinic, the patient was discharged to home with plans for ongoing outpatient speech therapy. Community reintegration can be the most challenging phase for a facial transplant patient, who must deal with identity, acceptance of body image, function, social roles and overall quality of life. The entire rehabilitation team plays a critical role in helping patients develop effective coping skills for everyday living.

**Lessons Learned**

Based on our experience with this first facial transplant, continuity of care throughout the rehabilitation process is critical, ideally with the same clinicians. Research, identification and implementation of new treatment modalities will be needed as more facial transplants are undertaken around the globe. Because most therapists lack experience working with patients with facial muscle and nerve injuries, and have little specialized training in facial muscle therapy, further education will be needed to ensure that patients receive competent care.
Functional neurosurgery is a subspecialty in which neurosurgeons target discrete regions of the brain and perform specific interventions (e.g., ablation, neurostimulation, neuromodulation) to relieve a variety of symptoms (e.g., pain, seizures, tremor, psychiatric distress) so that function is improved. The surgery is most often an elective procedure, the primary goal being to improve the patient's quality of life.

Perceptions of Surgical Success

Although the stated goals of functional neurosurgery are similar from both the surgeon's and patient's perspectives, there may be significant discrepancies in how each defines success. Most often, the medical establishment defines surgical efficacy using standard symptom rating scales that measure such variables as motor function, number of seizures and depression. These standard symptom rating scales may not fully correspond to the patient's goals and expectations for surgery, which often include increased control over one's life via attainment or resumption of specific behaviors and activities.

The goals of our studies involve a better understanding of, first, the evolving nature of patient beliefs about control and, second, the relationships between improvements in disease symptoms and the specific, individually defined behavioral goals and activities that compel our patients to seek out functional neurosurgery.

Identifying Control Types

We contend that up to three kinds of control are particularly important:

- **Symptom control** refers to one's ability to alter disease symptoms, such as tremor or number of seizures.
- **Personal control** refers to one's ability to autonomously and volitionally act to achieve personal goals. In personal control, the metrics are highly individualized and value laden, which makes them ethically interesting and central to informed consent.
- **Finally**, in some functional neurosurgery patients, such as those with implantable devices, device control is important. Device control refers to one's ability to adjust the actual stimulator settings.

Improvements in symptom or device control may or may not correspond to improvements in personal control. In order to provide better informed consent, it is important to recognize the challenges inherent in the shifting nature of personal control, which occur both before and after functional neurosurgery.

Study Methodology

To address these issues, we have designed a mixed methodology comprising both quantitative and qualitative measures. Generous funding from the National Institutes of Health supports our study of 50 patients with Parkinson's disease who are undergoing placement of deep brain stimulation (DBS) electrodes for treatment of their motor symptoms.

Study patients complete a set of standardized rating scales prior to surgery and at two points following surgery. In addition, all study patients participate in a series of three semi-structured interviews designed to gain a better and richer understanding of the important ethical themes that help shape patients' decisions regarding DBS surgery and therapy. This grant, titled "Ethics of Control and Consent in Brain Stimulation for Parkinson Disease," is the only bioethics grant funded by the National Institute of Neurological Disorders and Stroke through the 2009 challenge grant mechanism.

We are addressing similar questions in a population of patients undergoing neurosurgery for the treatment of intractable seizures. The Greenwall Foundation has provided generous support to our grant, "Ethics of Control and Consent in Patients Undergoing Epilepsy Surgery." The same mixed methodology is being used, with a combination of standard quantitative measures and qualitative data gleaned from semi-structured interviews in a sample of 36 patients who have undergone epilepsy surgery.

A Unique Collaboration

Through these studies, we expect to gain a better appreciation and deeper understanding of patients' goals and expectations for functional neurosurgery so that we can provide better informed consent. Further, we anticipate applying these data to better understand how to match goals of clinical research to appropriate understanding of control. Finally,
Most often, the medical establishment defines surgical efficacy using standard symptom rating scales ... These scales may not fully correspond to the patient’s goals and expectations for surgery, which often include increased control over one’s life via attainment or resumption of specific behaviors and activities.

these data will contribute to the development of ethically robust policy, research methods and clinical applications for emerging neurosurgical technologies.

These studies represent a unique collaboration between an academically trained philosopher currently working as a bioethicist and a neuropsychologist who has spent the past 18 years working with functional neurosurgery teams. This partnership is possible due to the importance placed on a multidisciplinary team approach—exemplified in Cleveland Clinic Neurological Institute’s center model—and strong collaboration from the Department of Bioethics. Moreover, this work illustrates the burgeoning field of neuroethics.

Cynthia S. Kubu, PhD, is a neuropsychologist in Cleveland Clinic’s Center for Behavioral Health and Center for Neurological Restoration. Her specialty interests include neuroethics, dementia and neuropsychological assessment in the neurosurgical treatment of epilepsy, movement, psychiatric and neurobehavioral disorders. She can be reached at 216.445.6848 or kubuc@ccf.org.

Paul J. Ford, PhD, is Director of Cleveland Clinic’s NeuroEthics Program, with appointments in bioethics, neurology and the Center for Neurological Restoration. His specialty interests include ethical issues raised by neurosurgical interventions, clinical ethics consultation and resident education. He can be reached at 216.444.8723 or fordp@ccf.org.

Postoperative X-ray showing placement of bilateral deep brain stimulation leads and electrodes in a patient with Parkinson’s disease.
A Multidisciplinary Approach to Sleep Disorders in Autistic Children
By Jyoti Krishna, MD, and Sumit Parikh, MD

Autism and related disorders, including Rett syndrome and Asperger’s disorder, are often associated with sleep disorders. Although sleep disorders are not currently included in the Diagnostic and Statistical Manual of Mental Disorders diagnostic criteria for autism spectrum disorder (ASD), an estimated 40 to 80 percent of children with ASD have sleep-related difficulties.

Sleep disorders are common even among higher-functioning patients with autism and those with ASD and normal intelligence quotients. Treatment of sleep disorders in this population may improve daytime behavior and mood, but it requires a global, comprehensive approach to address the interaction among medication, behavioral and psychological issues, and any underlying medical disorder that may affect sleep patterns. Therefore, the involvement of parents, primary care physicians, neurologists, psychologists and, in some cases, sleep physicians is critical to successfully managing sleep disorders and sleep-related issues in children with autism and ASD.

Behavioral Intervention
Insomnia is by far the most common sleep disorder associated with ASD, occurring in up to 70 to 80 percent of patients. Insomnia may involve bedtime settling difficulties; lack of sleep maintenance, with prolonged and problematic night and early morning awakenings; restless sleep; and failure to feel refreshed after sleep. Because patients lack the self-soothing ability that normally allows a return to sleep after natural awakenings, disturbed sleep patterns often repeat throughout the night.

The etiology of insomnia in ASD is varied, but behavioral dynamics between patient and caregiver are often implicated. In these cases, insomnia may be due to a lack of bedtime limit setting or detrimental sleep onset associations. With the former, there is failure to set firm boundaries, and the child learns to push limits and stall bedtime; with the latter, a special, comforting situation, such as the presence of a parent in bed, is required for the patient to fall asleep.

Interventions to alleviate insomnia may include adjustments to the sleep environment and to behavioral patterns surrounding bedtime routines.

Melatonin and Medication
Abnormal melatonin rhythms may contribute to insomnia in patients with ASD, who in some studies have been shown to excrete fewer melatonin metabolites in urine. However, there is no clinically available method for diagnosis of melatonin deficiency. Melatonin-related genetic defects may be associated with decreased activity of the acetylserotonin methyltransferase gene, which encodes the last enzyme of melatonin synthesis.

Melatonin supplementation is effective in some, but not all, children with ASD. Use of melatonin must be planned judiciously, in collaboration with physicians prescribing other medications that may have sedating effects. Melatonin treatment is generally most beneficial when paired with a program addressing home-based behavioral and environmental issues that may affect sleep.

Comorbid Disorders
Concomitant anxiety and mood disorders, attention deficit hyperactivity disorder and seizures in patients with ASD may contribute to sleep difficulties, and so may the medications used to treat them. Again, collaboration among all prescribers is essential to maintain medication regimens that avoid nighttime use of alerting agents, such as Ritalin, and to dose any sedating psychoactive agents closer to bedtime.

Patients with ASD may also have restless legs syndrome (RLS), periodic limb movement disorder, gastrointestinal complaints and obstructive sleep apnea, all of which can disrupt sleep. Referring
patients for diagnosis and treatment of these conditions may help reduce frequent awakenings and promote more restful sleep.

Treatment for sleep apnea, when not due to enlarged tonsils or adenoids, can be challenging in these patients, especially if continuous positive airway pressure (CPAP) is required. Resolution of CPAP-related challenges, including mask acceptance and adherence to therapy, may require psychological consultation.

Sleep Studies
In general, patients with ASD and insomnia do not require a sleep study. RLS is usually suspected through a thorough history of parental observation. However, when factors contributing to insomnia in ASD remain unexplained, a sleep study may be a necessary adjunct, especially if periodic limb movement and obstructive sleep apnea are suspected.
Sleep studies may also detect rapid eye movement disorder or parasomnias that occur later at night and are not observed by caregivers.

If a sleep study is desired, the facility must have experience with pediatric patients and be staffed with pediatric-friendly sleep technicians.

Autism Care Path
The incidence of autism has increased markedly in the past three decades, from approximately 1 in 2,500 to 1 in 150, with ongoing debate on whether this trend represents a true increase or simply reflects improved screening methods. In response to the disorder's prevalence, the Neurological Institute’s autism care path aims to standardize a comprehensive, multidisciplinary clinical approach to address all medical needs of patients with ASD, including diagnosis and treatment of sleep disorders.

Our care path is activated the moment a parent or pediatrician suspects autism. Patients are assessed by an Autism Center team headed by a psychologist and are screened for common neurological, metabolic, gastrointestinal, ophthalmologic and sleep disorders associated with ASD. Behavioral symptoms involving feeding, psychological and developmental issues are screened for as well, and genetic counseling and testing are discussed. If a child screens positively, a subspecialty referral is made to a provider interested and experienced in treating patients with ASD. These steps are in addition to any therapy-based treatments initiated.

The Neurological Institute is planning the creation of a database that will facilitate outcomes measurements to study whether subspecialty interventions, including those for sleep disorders, are of value in ASD treatment.

__Suggested Reading__


Using the rat model of spinal cord injury, the research team has shown that the combination of rolipram and liposomal clodronate promotes neuroprotection, enhances the sparing of myelinated tissue, and speeds and perhaps improves recovery of hindlimb function. The two agents are already in therapeutic use—clodronate in the United States, rolipram in Europe—a circumstance that may hasten the initiation of clinical trials.

Injury Toll Is Significant

Approximately 11,000 Americans suffer some form of spinal cord injury annually. The majority is young men between the ages of 16 and 30. (Men with the injury outnumber women 4 to 1.) Close to half (45 percent) of these injuries result from traffic accidents, while 34 percent derive from work and domestic accidents and 15 percent from sports injuries. The remaining 6 percent are self-inflicted or result from assault. In total, more than 200,000 Americans are living with aftereffects of the trauma. The National Spinal Cord Injury Statistical Center at the University of Alabama, the source of these data, estimates the cost at $4 billion a year.

Moderating the Post-Trauma Immune Response

The patient who suffers a spinal cord trauma can be said to be twice injured. The first injury is the trauma itself. The second derives from the actions of the immune response that immediately follows the initial trauma, and can continue for days or weeks.

Activated neutrophils, macrophages and monocytes infiltrate the wound to join activated microglia already present. These cells and others release a stew of cytokines and related factors that damage, rather than preserve, tissue within and adjacent to the trauma site. These factors attract and activate more immune cells that continue the destruction. The process eventually leads to formation of a glial scar enveloped in factors that appear to inhibit the regrowth and/or repair of injured neurons. (Some factors involved in the response appear to promote or stimulate axonal repair and growth, a puzzling dichotomy that is not yet understood.)

As research revealed details of the mechanisms driving the post-trauma immune response, the research team selected two drugs for their ability to moderate or inhibit aspects of that response. These agents were studied singly and in combination.

Clodronate is non-nitrogenous bisphosphonate, approved by the Food and Drug Administration to treat osteoporosis and hypercalcemia of malignancy. When encapsulated by liposomes, the drug induces selective apoptotic cell death in monocytes and phagocytic macrophages. Rolipram is a phosphodiesterase inhibitor, used in Europe as an antidepressant. The drug’s varied properties include anti-apoptotic effects and an ability to reduce the production of TNFα and ICAM-1, a factor that permits neutrophil adhesion.

Combinatorial Approach Is Effective

Our study began with 60 female Sprague Dawley rats undergoing moderate spinal cord injury. One group of animals, serving as controls, received DMSO delivered via a mini-osmotic pump. A second group received liposomal clodronate via intraperitoneal injection immediately following the injury and on post-injury days 1, 3 and 6. The third group received continuous infusion of osmotic rolipram with DMSO. The fourth group received a combination of liposomal clodronate and osmotic rolipram.

The group given the combination of the two agents evidenced the greatest benefits. While all groups showed some degree of recovery of function at four weeks, the animals receiving combination treatment began to evidence recovery as early as one week post-trauma. The treatment produced a comparative 51 percent reduction in overall lesion volume and a 69 percent reduction in the lesion at the trauma epicenter. There was a substantial reduction in ED-1+ (activated) macrophages/microglia within the injury and the surrounding spinal cord rim. There was also a substantial increase in the number of intact myelinated axons, accompanied by a reduction in myelin debris. Labeling at five weeks with the tracer Fluorogold showed there to be a significant increase in corticospinal axonal sparing and/or sprouting in the treated animals compared with the controls.
The research team believes these findings constitute a significant advance and a step toward clinical trials that may well demonstrate this combined drug approach can reduce trauma and speed recovery in patients with spinal cord injuries. Moreover, it is now within the realm of possibility that this treatment could be combined with evolving work with stem cells to further enhance recovery in these patients.

Michael Steinmetz, MD, is a neurological surgeon in Cleveland Clinic’s Center for Spine Health. His specialty interests include spine deformity, reconstructive spine surgery, spinal cord injury and peripheral nerve surgery. He can be contacted at 216.445.4633 or steinm@ccf.org.

REFERENCES


Now in its third year, the Knowledge Program has captured data from more than 1 million self-administered patient questionnaires. We are aggregating this patient-generated data with information from other sources, such as test results and providers, to optimize clinical decision making, quality improvement and research opportunities. Moreover, we are reporting our data as part of an organization-wide commitment to accountability and transparency.

Immediate Feedback

The electronic questionnaire that patients complete before each office visit comprises validated health status measures, both generic and disease-specific. The integration of these standardized quality-of-life measures with clinical data enables physicians to gain a more holistic view of patients’ overall health.

Initially, patients were asked to come early for their appointments to allow them time to complete the questionnaire. Now, they have the option of performing this task from home, work or virtually anywhere else with an Internet connection via MyChart, Cleveland Clinic’s secure online patient portal, or at one of the Neurological Institute waiting area computer kiosks the day of their visit.

Patient responses are incorporated in the electronic medical record, enabling the physician to review the results in advance and discuss them during the office visit. The physician can use data from the Knowledge Program to obtain a better view of the patient’s perceived health. We also use the results to plan and monitor treatment and identify the need for referrals.

Delivering relevant clinical information collected in the context of patient visits, the Knowledge Program has improved consistency of care across multiple sites in northeast Ohio.

Relevant, Accessible Data

One of our original goals in creating the Knowledge Program was to ensure that the data collected would be clinically relevant. The program meets this objective not only by capturing quantitative quality-of-life information, but also by allowing us to monitor patients’ illness severity over time and assess the efficacy of specific interventions to improve outcomes.

A second goal—to make the information readily accessible—is achieved through the interface with the electronic medical record. Every physician involved in an individual patient’s care has the opportunity to view that patient’s record and address issues such as pain, medication interactions or symptoms that are impacting the patient’s quality of life.

Customized Applications

Physicians in the Epilepsy Center have been involved with the Knowledge Program since its inception and now have data on some 3,000 patients, acquired in the course of 10,000 total patient visits—the world’s largest collection of quality-of-life and outcomes data on epilepsy patients.

Patients treated with anti-epileptic medications and those who undergo epilepsy surgery are queried on a range of issues beyond seizure frequency and severity. These include depressive symptoms, measured with the Patient Health Questionnaire (PHQ-9); anxiety, with the Generalized Anxiety Disorder (GAD-7) questionnaire; driving status; and overall quality of life, assessed on the Quality of Life in Epilepsy (QOLIE-10) scale.

This comprehensive assessment of overall health underscores the Epilepsy Center’s belief that the burden of this disease extends beyond a seizure count. These data help physicians perform a multidimensional evaluation of the patient’s treatment and its effect on quality-of-life issues specific to epilepsy. The information also facilitates early detection of psychosocial comorbidities such as depression and anxiety; thus, it helps identify epilepsy patients in need of treatment or referral for more detailed evaluations.

The Sleep Disorders Center was likewise involved with the Knowledge Program early in its development. Sleep disorders can affect quality of life in many ways, which is why patients seen by a sleep specialist are asked to complete a set of questionnaires that provide insight into their quality of life before and after treatment.

The Epworth Sleepiness Scale is used to assess the chance of dozing off during a sedentary situation, while the Fatigue Severity Scale is used to examine the effect of fatigue on daily activities. The Functional Outcomes of Sleep Questionnaire (FOSQ) assesses the
impact of sleepiness and tiredness in this patient population. FOSQ subscales can measure specific domains such as social outcomes, activity level and intimate relationships. The PHQ-9 can provide a possible explanation for why certain patients remain sleepy or tired after treatment, given that unrecognized depression may limit treatment response. Sleep Disorders Center physicians also track total sleep time for all patients before and after treatment.

The next initiative for the Knowledge Program is to use the data to develop disease-specific care paths. This quality assurance application will help ensure that each patient receives appropriate care.

Knowledge Program data document improvement in depression among adult epilepsy patients treated with medications. The Patient Health Questionnaire (PHQ-9) was used to screen for depressive symptoms. Mean PHQ-9 scores at first outpatient visit and last follow-up reflected a 17 percent reduction in severity, with greatest improvement among patients who were moderately to severely depressed at the outset.

Broadening Research Opportunities

Beyond its real-time implications for continuous improvement, the Knowledge Program is a rich source of data for clinical research. The Epilepsy Center and Sleep Disorders Center are in the early stages of organizing their data to generate outcomes research.

Physicians in the Epilepsy Center plan to use Knowledge Program data to identify the primary, independent determinants of quality of life in epilepsy patients. Sleep Disorders Center physicians will analyze changes in quality-of-life and depression scores after treatment for disorders such as sleep apnea, restless legs syndrome and insomnia.

Research is an emerging direction for the Knowledge Program, but our colleagues are using the program in their daily clinical practice and they value its impact on patient care.

The Knowledge Program is proving to be among our most constructive tools for delivering individualized care to improve outcome and quality of life for every Neurological Institute patient.
2010 – 2011 Continuing Medical Education

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

**JANUARY 29, 2011**

The Annual Therapy Symposium on Movement Disorders for the Modern Clinician: a 2011 Update (South Program)
Course Director: Hubert Fernandez, MD
Renaissance Port Everglades Hotel
Fort Lauderdale, Florida

**FEBRUARY 7-11, 2011**

(UPGRADE COURSE FEBRUARY 8-10, 2011)

Leksell Gamma Knife® Perfexion™ Course
Course Directors: Gene Barnett, MD, FACS, and John Suh, MD
Cleveland Clinic Gamma Knife Center
Cleveland Clinic main campus
Cleveland, Ohio

**FEBRUARY 25-27, 2011**

4th International Symposium on Stereotactic Body Radiation Therapy and Stereotactic Radiosurgery
Course Directors: Lilyana Angelov, MD, and Samuel Chao, MD
Disney’s Grand Floridian Resort
Lake Buena Vista, Florida

**APRIL 30, 2011**

Recognizing Parkinson’s Disease and Its Look-Alikes: a Symposium for the Primary Care Provider
Course Director: Hubert Fernandez, MD
DoubleTree Hotel
Independence, Ohio

**MAY 6, 2011**

7th Annual Contemporary Issues in Pituitary Disease
Course Directors: Amir Hamrahian, MD, and Robert Weil, MD
Cleveland Clinic Lerner Research Institute
Cleveland Clinic main campus
Cleveland, Ohio

**MAY 11-13, 2011**

Health Care Quality Innovation Summit: Optimizing Value and Securing a Future of Innovation and Quality
Intercontinental Hotel & Bank of America Conference Center, Cleveland
Cleveland, Ohio
ccfcme.org/quality11

**MAY 16-20, 2011**

(UPGRADE COURSE MAY 17-19, 2011)

Leksell Gamma Knife Perfexion Course
Course Directors: Gene Barnett, MD, FACS, and John Suh, MD
Cleveland Clinic Gamma Knife Center
Cleveland Clinic main campus
Cleveland, Ohio

**MAY 21, 2011**

Current and Emerging Uses of Botulinum Toxins in Neurology and Rehabilitation: A Comprehensive Full-Day Workshop
Course Directors: Hubert Fernandez, MD, Cleveland Clinic, and Kelvin Chou, MD, University of Michigan
InterContinental Hotel & Bank of America Conference Center, Cleveland
Cleveland, Ohio

**JULY 13-19, 2011**

Cleveland Spine Review Course
Course Directors: Edward Benzel, MD, and Douglas Orr, MD
Hyatt Hotel and Lutheran Hospital
Cleveland, Ohio

**AUGUST 8-12, 2011**

(UPGRADE COURSE AUGUST 9-11, 2011)

Leksell Gamma Knife Perfexion Course
Course Directors: Gene Barnett, MD, FACS, and John Suh, MD
Cleveland Clinic Gamma Knife Center
Cleveland Clinic main campus
Cleveland, Ohio

**OCTOBER 24-28, 2011**

(UPGRADE COURSE OCTOBER 25-27, 2011)

Leksell Gamma Knife Perfexion Course
Course Directors: Gene Barnett, MD, FACS, and John Suh, MD
Cleveland Clinic Gamma Knife Center
Cleveland Clinic main campus
Cleveland, Ohio

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

The Neurological Institute prioritizes its offer of new research developments and clinical therapeutic trials to patients with neurological problems. More than 225 clinical research trials are currently under way, with supported funding of more than $21 million. For more information on all our clinical trials, please call the Neurological Institute Research and Development office at 216.444.3507 or visit clevelandclinic.org/neurotrials.

BRAIN TUMOR

A Phase I Ascending-Dose Trial of the Safety and Tolerability of Toca 511 in Patients with Recurrent Glioblastoma Multiforme (GBM)

**Purpose:** This is a multicenter, open-label trial of the safety and tolerability of increasing doses of Toca 511.

**Eligibility:** Subjects between ages 18 and 75 with recurrent GBM who have undergone surgery followed by adjuvant radiation and chemotherapy.

**Principal Investigator:** Michael Vogelbaum, MD, PhD

**Study Coordinator:** Cathy Brewer; 216.444.7937; brewerc1@ccf.org

CENTER FOR NEUROLOGICAL RESTORATION

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

**Purpose:** This study is designed to evaluate the safety and efficacy of bilateral DBS of the ventral capsule/ventral striatum (VC/VS) as an adjunctive therapy for patients with a documented history of treatment-resistant depression. The study is a randomized, double-blind, sham stimulation-controlled, multicenter, prospective parallel-design study with two phases. Phase I, the feasibility phase, had FDA approval for enrollment and implantation of 30 subjects at five sites. This phase has been completed, and we are awaiting FDA data review completion for these first 30 subjects before we resume enrollment. While the FDA review proceeds, we continue to review records of patients interested in enrolling in this clinical trial.

The primary objective of this study, once enrollment resumes, is to demonstrate that improvement in depression among subjects in the active group (stimulation) is greater than among subjects in the control group (sham stimulation) after 16 weeks of therapy. The Montgomery-Asberg Depression Rating Scale scores of patients in the two groups will be used to determine improvement.

**Eligibility:** Patients 18 years of age or older with a primary diagnosis of treatment-resistant major depression, with the current episode lasting at least two years. Patients must have failed multiple trials of medications to treat their depression, including combination trials and augmentation trials. Patients will be excluded from the study if they have: a) a history of seizure disorder; b) a condition that will require diathermy treatments; c) a medical condition for which MRI is required or anticipated; d) met criteria for bipolar disorder, schizophrenia, schizoaffective disease, obsessive-compulsive disorder or psychosis; e) met criteria for substance abuse; f) a history of two or more suicide attempts in the last 12 months; g) been determined to be an imminent suicide risk; h) a diagnosis of myocardial infarction or cardiac arrest within six months of study enrollment; i) a history of a neurosurgical ablation procedure; j) a history of hemorrhagic stroke; k) a life expectancy of less than three years.

**Principal Investigator:** Donald Malone Jr., MD

**Research Nurse:** Rose Anne Berila, MSN, RN; 216.444.2673; berilar@ccf.org
Neurological Institute Select Clinical Trials

CEREBROVASCULAR

Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS)

Purpose: This study is a randomized clinical trial comparing stenting and intensive medical therapy vs. intensive medical therapy alone in patients with symptomatic intracranial arterial stenosis. All patients who are eligible and consent to study participation will be randomized to one of these two treatment arms. Patients in both arms of the study will be part of intensive risk factor management, which will consist of major efforts to meet protocol parameters for blood pressure control and low-density lipoprotein laboratory values as well as smoking cessation. Frequent office visits to monitor progress toward goals are provided for in the protocol. In addition, a lifestyle risk reduction program manager, provided for by the study, will contact patients frequently by phone to assess individual progress toward goals. Patients randomized to the stenting arm of the study will also undergo angioplasty and stenting of the offending intracranial artery.

Eligibility: Patients 30-80 years old who have had a transient ischemic attack or a non-severe stroke attributed to 70-99 percent stenosis of a major intracranial artery.

Principal Investigator: Irene Katzan, MD, MS
Research Coordinator: Nancie Tighe; 216.445.4488; tighen@ccf.org

EPILEPSY

Epilepsy Phenome/Genome Project: a Phenotype/Genotype Analysis of Epilepsy

Purpose: The Epilepsy Phenome/Genome Project (EPGP) is a collaborative research effort, funded by the National Institutes of Health (NIH) to understand the causes of epilepsy, why people respond differently to medications and why some families have several family members with seizures.

Eligibility: People with epilepsy who also have a brother, sister, parent or child with epilepsy. People with epilepsy due to: Infantile spasms, Lennox-Gastaut syndrome, Polymicrogyria or Periventricular heterotopia.

Principal Investigator: Jocelyn Bautista, MD
Research Coordinator: Jennifer Turczyk; 216.444.8638; turczyj@ccf.org

The Impact of Lacosamide on Wakefulness and Sleep in Adults with Focal Epilepsy: Searching for “Sleep-Friendly” Therapies for a Sleepy Population

Purpose: This Phase IV, randomized, single-center trial will objectively measure the effects of lacosamide (LCM) on sleep and wakefulness in adult patients with focal epilepsy. Subjects taking stable doses of one or two marketed anti-epileptic drugs (AEDs) for at least four weeks are randomized in a double-blind 4:1 scheme to LCM 400 mg/day or placebo, respectively. At the end of the treatment phase, subjects have the option to enter an extension phase in which they would receive LCM titrated to 400 mg/day or placebo, respectively. At the end of the treatment phase, subjects have the option to enter an extension phase in which they would receive LCM titrated to 400 mg/day. Subjects undergo polysomnogram and Maintenance of Wakefulness Test, keep a daily sleep/seizure diary, complete questionnaires, and undergo venipuncture and physical/neurological exams at study visits.

Eligibility: People aged 18 and older who are diagnosed with focal epilepsy with classifiable seizures per the International Classification. They should be deemed appropriate candidates for LCM adjunctive therapy and have been maintained on a stable dose of one or two marketed AEDs for at least four weeks.

Principal Investigator: Nancy Foldvary-Schaefer, DO
Research Coordinator: Judy Meinert; 216.445.7168; meinerj@ccf.org
MULTIPLE SCLEROSIS

Investigating FTY720 Oral in Primary Progressive MS (INFORMS)

Purpose: This study will compare the safety and efficacy of once-daily oral fingolimod (FTY720) 0.5 mg vs. placebo in primary progressive multiple sclerosis.

Eligibility: Aged 25-65, diagnosis of primary progressive MS, disease duration 2 to 10 years, EDSS 3.5-6.0.

Principal Investigator: Alexander Rae-Grant, MD
Research Nurse: Cynthia Schwanger, RN, BSN, MSCN, CCRP; 216.445.5788; schwanc@ccf.org

PEDIATRIC NEUROLOGY

Assess Specific Kinds of Children Challenges in Neurology Devices (ASK CHILDREN)

Purpose: This study assesses children's and families' perceptions of the impact of certain devices on their lives, in line with the FDA's quest for a more effective way to evaluate devices in children. A questionnaire is administered in conjunction with the FDA.

Eligibility: Children with a ventriculoperitoneal shunt, spinal cord stimulator post-spinal cord injury, deep brain stimulation for dystonia, vagus nerve stimulation for epilepsy or cochlear implant.

Principal Investigator: Neil Friedman, MBChB
Research Nurse: Diane Davies, LPN, BA, CCRP; 216.444.0713; daviesd@ccf.org

REHABILITATION

Use of Computer Gaming as an Adjunct during Outpatient Stroke Rehabilitation to Obtain Task-Specific Upper Extremity Practice Repetitions

Purpose: This pilot study will assess the effectiveness of providing additional repetitive, task-specific upper extremity practice using computer gaming as an adjunct to concurrent outpatient physical/occupational therapy post-stroke at three area hospitals (Cleveland Clinic main campus, Lakewood Hospital and Edwin Shaw Hospital for Rehabilitation). This study is being conducted in collaboration with Cleveland State University.

Eligibility: Individuals in outpatient physical and/or occupational therapy post-stroke; hemiplegic upper extremity with some degree of dysfunction post-stroke; cognitively able to learn to play game in three sessions or less; able to sit safely with back unsupported while playing Wii games.

Principal Investigator: Kathy Szirony, PT
Research Coordinator: Kathy Szirony, PT; 216.444.6432; szironk@ccf.org

SPINE

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

Purpose: This study aims to evaluate whether P-15 bone putty is not inferior in effectiveness and safety to local autologous bone when applied in instrumented anterior cervical disectomy and fusion with the use of a structural allograft ring in patients with degenerative cervical disc disease.

Eligibility: Men and women between the ages of 18 and 70 who will be undergoing anterior single-level fusion for degenerative disc disease with involved disc(s) between C3 and C7. Participants must have failed to gain adequate relief from at least six weeks of nonoperative treatment. Previous cervical surgery is an exclusion from this study.

Principal Investigator: Iain Kalfas, MD
Research Nurse: Diane Fabec, RN; 216.445.7744; fabecd@ccf.org
Cleveland Clinic Information

Referrals

General Patient Referral
24/7 hospital transfers or physician consults
800.553.5056

Patient referrals to all Neurological Institute physicians
216.636.5860 or toll free, 866.588.2264

On the Web at clevelandclinic.org/neuroscience

Services for Physicians

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

Referring Physician Center  For help with service-related issues, information about our clinical specialists and services, details about CME opportunities and more, contact us at refdr@ccf.org, or 216.448.0900 or toll free, 888.637.0568.

Critical Care Transport Worldwide  Cleveland Clinic’s critical care transport team and fleet of mobile ICU vehicles, helicopters and fixed-wing aircraft serve critically ill and highly complex patients across the globe. To arrange a transfer for STEMI (ST elevated myocardial infarction), acute stroke, ICH (intracerebral hemorrhage), SAH (subarachnoid hemorrhage) or aortic syndromes, call 877.379.CODE (2633). For all other critical care transfers, call 216.444.8302 or 800.553.5056.

Request for Medical Records  216.444.2640 or 800.223.2273, ext. 42640

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

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

Services for Patients

MyChart  MyChart is an online health management tool that securely connects Cleveland Clinic patients to portions of their medical records where they can view test results and medication lists, request new and review past appointments, and receive preventive care reminders to better plan the details of their ongoing healthcare. To sign up for a MyChart account, please visit ccf.org/mychart.

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

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

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