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NeuroFocus

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Jackson MEMORIAL HOSPITAL
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A physician's newsletter from the Departments of Neurology and Neurological Surgery at the University of Miami Miller School of Medicine in affiliation with Jackson Memorial Hospital

PENUMBRA Stroke System Being Used to Treat Acute Stroke Patients by our Neuro-Endovascular Service

Historically, patients have had limited options for the immediate treatment of ischemic strokes. Clot-busting drugs, such as tissue Plasminogen Activator (tPA), administered intravenously in the emergency room within three hours of the event, have been the only option.

Recent advances in the field of Neuroendovascular Therapy are allowing physicians to utilize cutting-edge devices, such as the PENUMBRA Stroke System, to expand the treatment window for acute ischemic stroke to eight hours, resulting in the prevention of permanent disability in many patients.

The Neuroendovascular service at the University of Miami Miller School of Medicine/Jackson Memorial Hospital (UM/Jackson), is a national leader in acute stroke intervention and is the only facility in Miami-Dade County equipped with two biplane neuroangiography suites, and also houses the largest stroke team that is ready 24-hour seven days a week to apply this brain saving therapy for patients with acute stroke.

The UM/Jackson Neuroendovascular service has been using the FDA-approved Penumbra Stroke System in their treatment of acute stroke patients in South Florida and it has resulted in numerous positive patient outcomes over the past three years. One such patient, Mr. George Mendes, a resident of the Florida Keys, experienced weakness on the entire left side of his body and face, along with slurred speech at about 6 pm on March 26, 2010. The patient was immediately taken to Mariner's Hospital in Tavernier, Florida, where ER physicians diagnosed him as suffering an ischemic stroke on the right side of his brain. They contacted UM/ Jackson's team of stroke experts and after consulting on the case, both groups of physicians agreed to administer tPA intravenously to the patient. Mr. Mendes did not show immediate improvement after the IV tPA resulting in a decision to arrange an airlift to Jackson Memorial Hospital (JMH) for more advanced treatment.

Mr. Mendes arrived by helicopter at JMH at 9:30pm. The symptoms had not improved and MRI imaging demonstrated a blockage in the right internal carotid and middle cerebral arteries. The decision was made to administer an emergency endovascular therapy utilizing the PENUMBRA device to attempt removal of the blood clots from the brain's arteries. At midnight, and still within the eight hour window of treatment utilizing neuroendovas-cular therapies, Dr. Dileep R. Yavagal, assistant professor of neurology and neurosurgery and director of interventional neurology at UM/Jackson, accessed Mr. Mendes' brain arteries through a small incision in his groin. Finding that the carotid artery and middle cerebral artery on the right side of his neck were completely blocked, Dr. Yavagal was able to navigate to the site of the right middle cerebral artery clot using the PENUMBRA system. Once there, he used the PENUMBRA device, approved by the FDA in 2007, to break up and aspirate the clot in the middle cerebral artery. This restored complete blood flow to the right side of the brain via cross flow from the left carotid artery.

Mr. Mendes improved rapidly in the coming days. He regained the ability to feel and move his left side. The slurring of speech and facial droop completely resolved. UM/ Jackson neurologists were able to determine that the stroke had been caused by an irregular heartbeat, which sent blood clots to the Mr. Mendes' brain and produced the blockage. He was started on Coumadin for stroke prevention and after a two-week stay at JMH, he was discharged with almost no residual effects.

Dileep R. Yavagal, M.D., assistant professor of clinical neurology and neurosurgery, exhibiting the PENUMBRA device that is used for the removal of the blood clots from the brain's arteries.

The UM/Jackson Neuroendovascular service, which includes Drs. Dileep Yavagal and M. Ali Aziz-Sultan, assistant professor of clinical neurological surgery, leads the region in providing such cutting-edge, brain saving care and is ready to help patients restore critical neurologic function threatened by acute stroke.

Since January 2008, more than 100 patients with endovascular therapies for acute stroke have been treated at Jackson Memorial Hospital and University of Miami Hospital. Over more than 50 of these patients were treated with the PENUMBRA Stroke System with a 70-80 percent rate of successful opening of the blocked artery in the brain. ■

WHAT'S INSIDE

The University of Miami/Jackson Memorial Hospital departments of Neurology and Neurosurgery are ranked #29 in the nation by US News & World Report's Best Hospitals 2010.

Clinical Trials

NEUROLOGY

REDUCTION IN THE PROGRESSION OF ALS THROUGH ARIMOCLOMOL

(ALS) Amyotrophi Lateral Sclerosis, often referred to as Lou Gehrig's Disease, affects approximately two out of 100,000 people each year from all age groups, races and ethnic backgrounds. Typically, ALS onset occurs between 40 and 60 years of age, but younger and older people can also develop the disease. Familial ALS (fALS) accounts for approximately 5–10 percent of all ALS cases and is caused by genetic factors. Of these, approximately 1 in 10 is linked to a mutation in the superoxide dismutase (SOD1) gene. The primary study objective is to demonstrate the efficacy of arimoclomol, an inducer of heat shock protein gene expression, in people with rapidly progressive SOD1 positive familial ALS who harbor specific mutations in the superoxide dismutase-1 (SOD1) gene. The primary hypothesis is that arimoclomol will reduce by at least 30 percent the rate of progression of disease as measured by changes in the revised ALS functional rating scale (ALSFRS-R). A total of 30 participants will be enrolled in the Phase II component of this study, with an additional approximately 50 subjects enrolled in the phase III component.

PI - Michael Benatar, MD, PhD

For more information on Neurology clinical trials please call 1-877-977-7724

NEUROLOGICAL SURGERY

Traumatic Brain Injury

TBI BIOMARKERS

A study is currently underway to evaluate the severity of TBI and its outcomes using paired cerebrospinal fluid and serum. These samples are analyzed in people immediately post-injury and compared with brain injury severity and outcome. The project aims to find a panel of six to twelve sensitive and specific biochemical serum or TBI markers that will allow the rapid diagnosis of TBI and aid in the assessment of therapeutic interventions aimed at TBI. Current results show a positive correlation between the extent of TBI and specific biomarkers, thus allowing earlier intervention and management.

PI – M. Ross Bullock, MD, PhD

Stroke

Retrospective Analysis of Endovascular Therapy for Acute Ischemic Stroke: Importance of Pre-procedural Perfusion Studies

The purpose of the study is to determine the clinical outcomes of the impact of perfusion imaging after endovascular therapy for acute ischemic stroke (AIS).

The study anticipates that the selection of AIS patients with advanced perfusion imaging will lead to decreased intracerebral hemorrhage (ICH) as compared to AIS patients with non-contrast CT. The study is retrospectively reviewing all cases of acute anterior circulation ischemic stroke undergoing endovascular intervention at Jackson Memorial Hospital over a 28-month period. The study is determining the post-revascularization hemorrhagic transformation rate of acute ischemic stroke patients before and after the availability of advanced perfusion imaging at our institution.

PI – M. Ali Aziz-Sultan, MD

For more information on Neurological Surgery Clinical trials please call 1-800-996-3783

One Year Later

A Continuing Commitment to Haiti

It has been more than a year since a powerful earthquake devastated Haiti and caused widespread destruction. In the *NeuroFocus* spring 2010 issue we gave you a glimpse into the efforts by the University of Miami's team of neurologists and neurosurgeons treating patients with everything from spinal cord injury to stroke.

Just 20 hours after the earthquake, Barth A. Green, MD, chairman of the Department of Neurological Surgery and founder of Project Medishare, and his team touched down in Port-au-Prince and were faced with death, carnage and hundreds of injured. In addition to their effort, more than 5,000 doctors and nurses traveled to Haiti, treating more than 65,000 patients in tent hospital facility during the months following the disaster.

Today, Project Medishare has partnered with Hospital Bernard Mevs in Port-au-Prince to create a state-of-the-art facility with several sterile surgical theaters, and an infant and pediatric intensive care unit. The hospital now provides all of its services free of charge. Thousands have been served by this hospital.

Despite the improvements that have been made, Dr. Green said there still needs to be a massive fundraising campaign in the U.S. and in other countries to assist with the long-term recovery of Haiti. ■

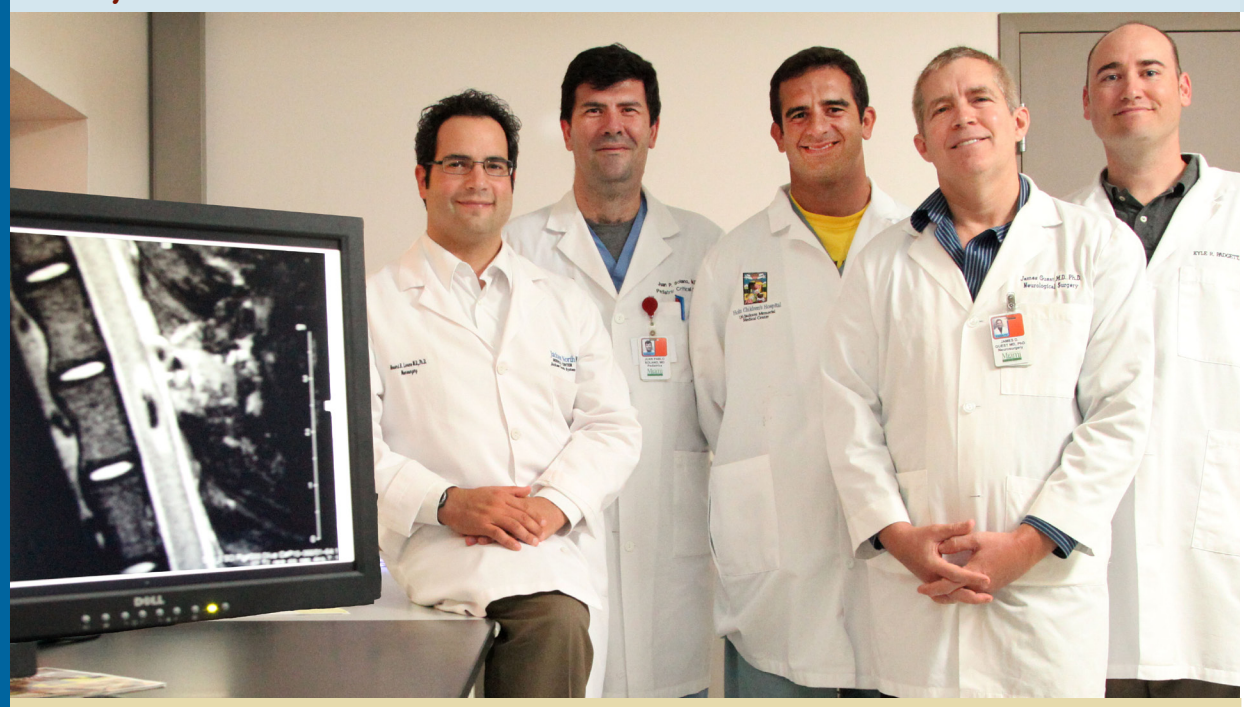
UM Global Institute/
Project Medishare for Haiti

www.projectmedishare.org

Allan D. Levi, MD, PhD, professor of neurological surgery, published an article about the Miller School's experience in Haiti after the 2010 earthquake in the winter 2011 issue of *Congress Quarterly*, the official newsmagazine of the Congress of Neurological Surgeons. The article, titled "The Early Response," chronicled the unprecedented medical relief effort in the days and weeks after the quake.

Pig Model Generates Critical Pre-Clinical

By Kim Anderson-Erisman, Ph.D.



The micropig team (from left): Howard Levene MD, PhD, Juan Solano, MD, Manny Gonzalez-Brito, DO, James Guest, MD, PhD, and Kyle Padgett, PhD. *Photo by: Rob Camarena*

As part of our Clinical Trials Initiative, investigators at The Miami Project to Cure Paralysis have created a large animal model of spinal cord injury (SCI) to answer critical, clinically relevant questions regarding translation of results discovered in rodents to humans.

This is especially important for interventions involving surgical procedures, such as cell transplantation. A pig model of SCI is being used because its spinal cord is larger than rats and more comparable to the human spinal cord. The rat thoracic spinal cord area is approximately .1 to .2 times that of the human spinal cord and the porcine (pig) thoracic spinal cord area is approximately .5 to .6 times that of the human spinal cord.

Department of Neurology Receives Award
for the Study of Muscular Dystrophy

Antonio Barrientos, PhD, associate professor of neurology and biochemistry and molecular biology at the University of Miami Miller School of Medicine, is the recipient of a three year research award totaling $346,500 from the Muscular Dystrophy Association to study the underlying molecular mechanisms in some forms of mitochondrial myopathies. For this project, the research team directed by Dr. Barrientos will include Neurology Assistant Scientist, Dr. Flavia Fontanesi and biochemistry PhD candidate, Jingjing Liu.

In patients diagnosed with one of the mitochondrial myopathies, cellular energy production is severely compromised, affecting brain, muscle and other organs with high energy demands. One of the most frequent causes of mitochondrial myopathies involves alterations in the biogenesis and function of the cytochrome c oxidase (COX). COX is the last enzyme of the mitochondrial respiratory chain, and it is essential for cellular respiration and aerobic energy production. The enzyme is formed by 13 protein subunits of dual genetic origin. The three subunits forming the catalytic core of the enzyme are encoded in the mitochondrial DNA, and the rest are encoded in the nuclear genome. The assembly of all these proteins to form a functional enzyme is complex and requires the assistance of more than 30 ancillary factors, most of them conserved from yeast to human. Mutations in the structural subunits and the assembly factors cause severe mitochondrial myopathies in humans. To fully recognize the molecular basis behind these diseases, Dr. Barrientos and his colleagues have been conducting research on COX biogenesis over the last 12 years with the continuous support of the MDA. Using a yeast research model, they recently identified two new "chaperone" proteins required essential steps on the biogenesis of the COX enzyme.

Currently, the UM team of researchers is planning to study the corresponding two yeast proteins in human cell lines to examine whether their functions are conserved. Utilizing a gene silencing technique to deactivate the expression of genes coding for these chaperones, the scientists will be able to hinder the proteins' production allowing them to observe and characterize the phenotype resulting from their absence.

(From left) Jingjing Liu, biochemistry PhD candidate, Flavia Fontanesi, neurology assistant scientist, and Antonio Barrientos, PhD, associate professor of neurology, examine the COX enzyme as part of the muscular dystrophy study.

Dr. Barrientos has previously conducted other research studies funded by the MDA, with a total of more than $1.2 million including the present award. These studies have yielded notable contributions to scientists' understanding of the dynamics involved in COX production and the regulation of its biogenetic process. The two genes identified are new candidates when screening for genes responsible for mitochondrial myopathies associated with COX deficiency in patients. The UM team's newly funded project could possibly yield results that would help produce therapeutics to target these genes and their protein products. ■

Safety Data for Schwann Cell Transplantation Trial

These size characteristics enable the use of this model for detailed safety studies of injection parameters and subsequent translation of these parameters to human application. Hence, Miami Project investigators, in collaboration with a team of pediatric intensive care specialists at the University of Miami initiated by John Kuluz, MD, have developed a micropig contusion injury model.

The surgical procedures required for this animal model are virtually identical to those required for human surgery. Neurosurgeons James Guest, MD, PhD, and Howard B. Levene, MD, PhD, provide the expert surgical skills necessary to make this model relevant, reproducible, and ethical.

Control of the anesthesia is another huge factor. The expertise of our pediatric intensive care specialists, Juan Solano, MD, and Manny Gonzalez-Brito, DO, have enabled this project to move forward successfully. Other critically important components are animal care and behavioral assessment. Factors that are measured to evaluate safety include neurologic assessment, walking, somatosensory and motor evoked potentials, which measure the "connectedness" of the neural circuitry from the sensory nerves in the legs through the spinal cord to the sensory cortex of the brain, as well as magnetic resonance imaging (MRI) to measure lesion volume, bleeding, inflammation, and the effects of making an injection.

These volumes measured by the MRI may aid in determining the dose and volume to be implanted. After the cell injection is made, the MRI allows several important variables to be assessed, including spinal cord swelling, injection-related bleeding, and a new concept called hydrodynamic dissection, which indicates that the injection pressures were excessive. MRI is important because it provides near-immediate feedback about the effects of injection. By correlating the changes visible on MRI with the changes in spinal cord conduction of evoked potentials, and changes in the porcine walking scale, we can help ensure that human spinal cord injections are made with much greater safety than would be possible without these studies.

The Miami Project is utilizing this model to generate critical pre-clinical safety data for our proposed clinical trial involving Schwann cell transplantation. Specifically, this model is being used to closely imitate human clinical conditions in safety evaluations of injection volume, cell concentration, needle size and profile, manner of cord perforation, rate to needle depth, injection rate, post-injection dwell stabilization time, and needle withdrawal time. These studies are being conducted by a team led by Drs. Guest, Levene, and Solano.

Critical discoveries have been made regarding the volume of cells that can be injected into the injury site without causing harm as well as the rate of injection. The Miami Project has been collaborating with experts at Geron Corporation, who have begun a Phase I clinical trial injecting embryonic stem cells into the spinal cord of acutely injured individuals, to optimize a syringe positioning and injection device for safer cell transplantation.

The Miami Project is also utilizing this large animal model to conduct pre-clinical studies to identify the optimal methods for delivering Rolipram as a neuroprotective therapy for acute SCI. These studies are being led by Damien Pearse, PhD and are carried out by members of the porcine SCI team as well as Cheng-Chih Liao, PhD within the Pearse laboratory. The work follows on from results published in 2004 by Dr. Pearse and Mary Bunge, PhD, demonstrating the beneficial effect of combining rolipram with Schwann cells and cyclic AMP in laboratory rats with SCI. Porcine studies are being employed to examine the safety, toxicity, and efficacy of Rolipram as an acute neuroprotective agent in a larger animal model of SCI. For these studies, animals receive a contusion injury to the thoracic spinal cord and within hours an intravenous (IV) infusion of rolipram or a control solution (placebo) is given. Additional administration of Rolipram is provided during the first two weeks following injury. Preliminary results indicate that IV administration of Rolipram for two weeks after SCI appears to be safe. The early results of these experiments are promising and their completion will guide us in preparing to submit an IND application to the FDA for a future clinical trial.

Obviously, it takes a significant amount of manpower and expertise to make this animal model a successful tool. Factors critical to success include excellence in anesthesia; surgical technique; animal care; behavioral testing; electrophysiology, and access to state-of-the-art equipment, such as MRI and injection devices. The academic environment at the University of Miami Miller School of Medicine is tailor-made for this truly collaborative research effort. ■

NeuroFocus

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In The News

Michael Benatar, MD, PhD, Joins the Department of Neurology

Dr. Benatar has recently joined the neuromuscular team as an associate professor of neurology and epidemiology and the chief of neuromuscular division. Previously the co-director of the Muscular Dystrophy Association Clinic at Emory University, he received his medical degree in South Africa and his PhD from Oxford University where he spent three years as a Rhodes Scholar. He completed his clinical training in neurology, neurophysiology and neuromuscular disease at Harvard University and holds a Master's degree in the Science of Clinical Research from Emory.

Dr. Benatar's clinical and research interests include (ALS) Amyotrophi Lateral Sclerosis and myasthenia gravis. He is currently investigating the epidemiology of ALS, exploring novel ALS biomarkers and leading a multicenter clinical trial for patients with familial ALS. He is also initiating a multicenter clinical trial for patients with ocular myasthenia.

Ryan Trombly MD, Receives University of Miami Hospital Consultant of the Year Award

The University of Miami, Division of Hospital Medicine faculty, presented Dr. Trombly with the Consultant of the Year award during an honorary reception on Saturday, December 11, 2010. The annual award is bestowed upon a UM faculty member who best exemplifies the level of communication needed to deliver world class service to UM patients and who best fulfills the Ten Commandments of Medical Consultation. These include adhering to the importance of relationship building with referring-physicians, communicating succinctly and administering detailed patient follow-up.

What's Next

UM Hosting Fourth Annual McKnight Brain Research Foundation Inter-Institutional Meeting

May 1-3, 2011

The Evelyn F. McKnight Brain Institute team at the University of Miami Leonard M. Miller School of Medicine will be hosting the Fourth Annual McKnight Inter-Institutional Meeting being held at the Miami Beach Resort and Spa, May 1 to 3, 2011. This institute member only meeting, entitled "Reducing the risk of age-related memory loss," brings together about 100 faculty and researchers from the four McKnight Brain Research Foundation (MBRF) Funded Institutions, located in Florida, Arizona and Alabama, to discuss new and exciting findings in age related memory loss.

Neurological Surgery Clinic Opening at UHealth Hialeah

June 2011

Dr. M. Ross Bullock, MD, PhD, Professor of Clinical Neurological Surgery, and Ronald Benveniste, MD, Assistant Professor of Clinical Neurological Surgery, will begin operating a clinic in the Miami region of Hialeah beginning in June of this year at UHealth Hialeah, 7000 West 12th Avenue, Suite 4, Hialeah-Miami Lakes, Florida 33014. This location will allow patients and referring physicians in the area to have a more convenient resource for neurosurgical care. All surgeries will continue to be performed at University of Miami Hospital or Jackson Memorial Hospital.

High Tech Multimodal Neuro-Monitoring Intensive Care Unit

Jose Sanchez, M.D.

Dr. Jose Sanchez, neurosurgery head trauma fellow, has created the capability to store and integrate data from the standard Intensive Care Unit (ICU) SpaceLabs monitors with new high tech neuromonitoring machines such as cerebral microdialysis, brain oxygenation and electrocorticography.

Dr. Sanchez organized a multidisciplinary team composed of engineers and technicians from Biomed, Jackson Memorial Hospital IT and companies such as SpaceLabs, CMA/Microdialysis and Moberg Research, Inc., to ensure the communication and storage of the integrated Multimodal brain monitoring data. Mr. Luciano Guglielmi, from the Jackson IT department, also played an integral part in this achievement.

The tool's success was shared at the meeting entitled "Clinical Integration of Tomographic and Physiological Imaging and Multimodal Monitoring – Present and Future" held in Santa Fe, New Mexico (August 26-28, 2010). Dr. Sanchez presented with Kristine O'Phelan, MD, assistant professor of clinical neurology, Ross Bullock, MD, PhD, clinical director the neurotrauma program, and Dalton Dietrich, PhD, scientific director of the Miami Project to Cure Paralysis.

This integrated tool allows for better analysis and subsequent management of the complex pathophysiology of patients with severe TBI and other neurological diseases in the Neuro ICU at Jackson Memorial Hospital. With this capacity of multimodal integration, our neuroscientists can participate in future multicenter studies and are further equipped to implement the Neuro ICU database.

As a result of Dr. Sanchez's achievement, Dr. Bullock has invited him to be a chapter co-author for the "Development of Acute Care Guidelines and Effect on Outcome" in the 2nd edition of the book "Brain Injury Medicine: Principles and Practice".

Dr. Sanchez has also developed a digital patient's daily progress note as part of the project. He is collaborating with the Jackson Advance Clinical Knowledge System (JACKS) team to implement a similar automatic daily progress note from Cerner, a healthcare information company, to help in the efficiency and quality of the daily work of interns, residents and fellows in the UM/Jackson medical system.

Dr. Jose Sanchez examining data of a severe TBI patient using the multimodal neuromonitoring system.