Responsive Neurostimulation (RNS) Offers New Hope to Patients with Intractable Epilepsy

by Danielle Wagner, PA-C and Mark Richardson MD, PhD, FAANS

“No I feel like, yes, I have epilepsy, so what?” These are the words used by our first patient at UPMC to undergo implantation of the Responsive Neurostimulation (RNS®) device, to describe her improved outlook on life. Many patients with epilepsy do not receive a referral to an academic epilepsy center, where the most modern diagnostic and therapeutic options are available, and subsequently are left feeling ashamed about their disease and its effects on their lives. For those patients that do eventually make it to an epilepsy surgeon, this referral happens on average almost 20 years after they have been diagnosed. Surgical resection of the seizure focus remains the best treatment for intractable epilepsy, but despite our best efforts and often an exhaustive work up, we are unable to offer resective surgery to some patients. Patients that have bilateral seizure foci or a seizure focus in eloquent cortex that is not amenable to resection have had very few treatment options, and for this reason the FDA approval of the RNS device in November 2013 was an important and exciting development.

RNS is now approved to treat adult patients with intractable partial onset epilepsy who have frequent and disabling seizures localized to one or two foci. RNS is a closed-loop device that continuously monitors electrocorticography via one or two implanted strip or depth electrodes. The neurostimulator delivers a brief pulse of electrical stimulation directly to the seizure onset zone when a seizure or seizure-like activity is detected. The neurostimulator itself is placed under the scalp and is nested within the skull, requiring a full-thickness craniectomy. This technology represents a significant advancement from current clinically approved neurostimulation devices, such as deep brain stimulators (DBS), which do not possess the ability to record and respond to brain function.

Another unique feature of RNS is the role each patient plays in his or her treatment. Each patient is given a remote monitor, essentially a laptop computer, to which they must download the information stored on their neurostimulator on a daily basis.

(Continued on Page 8)
Chairman’s Message

Being Part of Neurosurgical History and Developing the Future of Neurosurgery

In our 79-year history, the Department of Neurological Surgery at the University of Pittsburgh has played a key role in developing and enhancing many aspects of neurosurgery, most notably Gamma Knife® radiosurgery, novel skull base approaches, microvascular decompression for a variety of cranial nerve ailments, expanded endoscopic endonasal surgical approaches, and spine radiosurgery.

We are extremely proud of the impact we have made in the field. However, we also realize, and whole-heartedly embrace, the responsibility and challenge of continuing to innovate and write the future of neurosurgery.

With this goal in mind, our department remains a robust driver of innovation. Our goals are broadly encompassing, including a commitment to providing the very best care to our patients, to improving neurosurgical care through research and ingenuity, and to training the next generation of neurosurgical academic leaders.

Key conditions remain at the forefront of innovation, including the development of minimally invasive methods for the resection of difficult-to-reach skull base lesions, creating viable brain-machine interface approaches, perfecting minimally invasive approaches to the spine, creating new diagnostic and management paradigms for traumatic brain injury, as well as developing novel neuroprotective approaches for the brain and spinal cord.

As part of shaping neurosurgery, we are fully committed to training the future generation of academic neurosurgical leaders. Our residency program reached an important milestone recently by becoming the largest in the nation. The size and scope of our program affords us the unique opportunity to expose our trainees to a greater variety of surgical procedures and to tailor their education to their specific interests. Our residents now have a greater ability to dedicate protected time to either laboratory work or to engage in subspecialized enfolded fellowships. Furthermore, our residents are securing some of the most prestigious and competitive post-residency fellowships.

Our department cannot be complacent in having played a critical role in neurosurgical history. It is our desire and responsibility to continue to write it. We come to work every morning to provide the best care for our patients, to teach the next generation of neurosurgical academic leaders, and to write the future history of neurosurgery.

Robert M. Friedlander, MD, MA
Chairman and Walter E. Dandy Professor of Neurological Surgery
Co-Director, UPMC Neurological Institute
Avoiding Surgical Site Infections: A Must for All!

by D. Kojo Hamilton, MD

Surgical site infections (SSIs) in spine surgery have significant implications to the patient. The National Healthcare and Safety Network report from 1,545 hospitals during 2006-2008 had an overall spine surgical site infection rate of approximately 1.3%. This ranged from ~1% in spinal laminectomy surgery to a high of 3.1% in revision spine surgery involving a fusion procedure. SSIs following spine surgery are concerning for delayed recovery, success of surgery, readmission, and reoperations. There is also delayed return to work as well as the financial cost. There continues to be a pressing multidisciplinary effort to reduce, if not eliminate, surgical site infections.

Efforts to reduce SSIs include participation from all, beginning with the patient, surgeon, and hospital. The modifiable factors aimed at reducing SSIs are based on time categories: preadmission, preoperative (before incision), intraoperative, and postoperative. Preventing spine surgery infections starts with optimizing patients prior to surgery with reduction of bacterial burden. It is imperative to maintain perfusion of healthy tissues intraoperatively, and to also eliminate contamination with advanced sterilization techniques as well as the use of perioperative antibiotics.

Organisms that continue to dominate the lists of pathogens causing surgical site infections of the spine, as well as bony infections of patients, include Staphylococcus aureus (~49%) and Coagulase-negative Staphylococci (~14%).

Transmission pathways for Staphylococcus aureus include hematogenous (from contaminated blood or via infected organs), exogenous (e.g., from hospital equipment, health care workers, other patients), and endogenous sources (patient’s nares, skin, and other surfaces).

Efforts to enhance the modifiable factors mentioned above include optimizing medical conditions prior to surgery, especially in diabetics (good control currently equals preoperative HgB A1c < 8, recent glucose <200) and smoking cessation (stop at least 4-8 weeks prior to surgery). Body mass index greater than 40 is also associated with an incremental risk of spine infections.

In the perioperative period, current efforts to decrease surgical site infections include screening and eradication. The hypotheses behind screening patients is that patients who are carriers have endogenous and sometimes virulent strains of pathogens associated with spine infections. Efforts to minimize spread include sampling and testing for bacteria of specific reservoirs such as the patient’s axilla, groin, perianal, and nares with cotton swabs. Up to 30% of the adult population in the community are at some point colonized with Staphylococcus aureus, with up to 5% of those with drug-resistant strains.

UPMC’s neurological surgery spine center is one of the few centers currently enrolling patients for a promising vaccine for several of the more common and resistant strains of Staphylococcus aureus. This is a testament to the medical center’s commitment to being at the forefront of any innovation contributing to the improvement of patient care.

Prior to surgery, decolonization and reduction of bacterial burden efforts include preoperative showers, and the relatively inexpensive and low-risk use of sage cloths infused with 2-4% chlorhexidine gluconate. The topical use of the bacteriostatic agent mupirocin nasal ointment prior to surgery in addition to use of sage cloths, has shown effective decrease in SSIs related to resistant Staphylococcus aureus. Nevertheless, it is prudent to cancel spine surgery if immediate preoperative assessment shows excessive skin breakdown or acne associated with propionibacterium spp infections. At UPMC, our astute preoperative nurses perform a secondary assessment to ensure that the skin has no obvious lesions.

Intraoperative preparations include skin antiseptic preps as well as systemic antibiotics. Our hospital system continues to exceed the required air quality and operative room laminar flow requirements. In addition, tracking by our infection control team for deviations in protocol (sterilization, hand hygiene) or procedures is vigorous, leading to lower than regional and national average of spine surgery related infections among tertiary care centers.

Postoperatively, ways to reduce SSIs include early removal of drains and catheters, and use of occlusive dressings.

In conclusion, SSI prevention involves a significant removal from all stakeholders, including patients and caregivers, with constant vigilance and with adherence to protocols, as well as best attempts to reduce patient risk and exposure prior to spine surgery.
2015 CNS: Annual Meeting Presentations

University of Pittsburgh Department of Neurological Surgery faculty and residents presented and participated in numerous seminars, courses, presentations, and lectures at the recent Congress of Neurological Surgeons (CNS) Annual Meeting in New Orleans, La., September 26-29. Following is a list of faculty and resident participation.

Practical Courses

**3-D Surgical Neuroanatomy (Supratentorial).** Course Director: Fernandez-Miranda JC. Faculty: Avci E, Blackburn SL, Cohen-Gadol AA, De Oliveira E, Rubino PA, Sorenson JM, Tune U.

**3-D Surgical Neuroanatomy (Infratentorial).** Course Director: Fernandez-Miranda JC. Faculty: Benes V, Blackburn SL, Cohen-Gadol AA, De Oliveira E, Rubino PA, Sorenson JM, Tanriover N.

**Building a Neurosciences Program.** Course Director: Steven A. Tomes. Faculty: Brosious M, Ecklund JM, Friedlander RM, Pracyk JB, Ratliff JK, Faculty: Brosious M, Ecklund JM, Friedlander RM.

**Trauma Update: Traumatic Brain Injury.** Course Director: Carney N, Siddiqui AH, Steinberg GK.

**Practical Courses**

**Section Presentations**


**Oral Presentations**

A Cost-effectiveness Comparison Between Open Transforaminal and Minimally Invasive Lateral Lumbar Interbody Fusions Using the Incremental Cost-effectiveness Ratio at 2 Year Follow-up. Gandhoke GS, Shin HM, Chang YF, Tempel ZJ, Okonkwo DO, Gorszten PC, Kanter AS.


**Symposia**


New Frontiers and Innovations in Radiosurgery. Moderator: Friedman WA. Faculty: Niranjan A, Pekar S, Pollock BE.

**Poster Presentations**

Applicant Cost for Residency Match in Neurological Surgery. Agarwal N, Choi PA, Okonkwo DO, Barrow DL, Friedlander RM.


(Continued on Page 6)
Select CNS Meeting Abstracts

Predictive Value of Changes in Intraoperative Neurophysiologic Monitoring During Intracranial Aneurysm Embolization

Ares WJ, Grandhi RM, Crandall DJ, Habeych ME, Thimulala PD, Horowitz MB, Javin TG, Jankowitz BT, Bolzer J, Ducruet AF

Objective: Intraoperative neurophysiologic monitoring (IONM) has been utilized to detect and prevent neurological complications during many neurosurgical procedures. However, few reports exist describing its use during neuroendovascular procedures. In this study, we examined our single-center experience using IONM, specifically the use of somatosensory evoked potentials (SSEP), during endovascular embolization of intracranial aneurysms.

Methods: A retrospective review of a prospectively collected database was carried out encompassing consecutive patients undergoing intracranial aneurysm embolization with concurrent SSEP monitoring from January 2006 to August 2012. Both ruptured and unruptured aneurysms were included. Hospital records were reviewed to collect patient demographics, procedure related data and the presence of a new neurologic deficit at 24 hours post procedure.

Results: Among 888 patients, 77 experienced SSEP changes and 28 had new post-procedural neurologic deficits (PPND). The positive and negative predictive values of a change in SSEP monitoring indicating a PPND were 27% and 99%, with a specificity and sensitivity of 75% and 93%, respectively. Compared to a population without SSEP changes, a 50-99% loss in SSEP waveform was associated with a 20-fold increase in risk of PPND and 100% loss of SSEP waveform, regardless of return, was associated with a greater than 200-fold risk of PPND.

Conclusions: This study represents the largest experience of the use of IONM during endovascular embolization of aneurysms. We have found that SSEP changes demonstrate a high sensitivity for clinically relevant ischemic events during these cases; additionally, magnitude and persistence of SSEP changes is correlated with risk of PPND. Although further analysis of the clinical outcomes of patients who experience changes in IONM is necessary, its use may provide a key safety measure during endovascular aneurysm embolization by providing the physician with important feedback and allowing the opportunity to respond to intra-procedural changes in monitoring to minimize post-procedural clinical deficits.

The Relationship Between Frontal Lobe Surgery and Hippocampal Inflammation and Neurogenesis Inhibition on Cognitive Dysfunction in a Rat Model


Introduction: Although postoperative cognitive dysfunction (POCD) is a known complication after intracranial surgery, the underlying causes are largely unknown. Impaired hippocampal neurogenesis following radiation and chemotherapy has been associated with cognitive dysfunction in animal models. In this investigation, hippocampal changes after frontal lobe surgery that might be involved in POCD were examined.

Materials and Methods: Under general anesthesia, a frontal lobe corticectomy was performed in 10 adult Windstar rats (Group 4; G4). Three different control groups included animals without any treatment (G1), animals placed under general anesthesia alone (G2), and animals undergoing a craniectomy without opening the dura (G3) (n=10 each). Twenty-four hours after surgery, half of the animals were sacrificed, and the mRNA levels for IL-6, TNF-α and BDNF in the contralateral hippocampus were assessed by qPCR. Seven days later, the remaining animals underwent anxiety (high plus maze) and memory (novel object recognition) testing. All animals were then sacrificed, and the number of immature neurons in the hippocampal cortex was measured by doublecortin staining.

Results: Twenty-four hours after surgery, the mRNA levels of IL-6 and TNF-α increased and BDNF decreased in both surgical groups G3 and G4 (p<0.05). Cognitive tests demonstrated an increase in anxiety levels and memory impairment in both G3 and G4 compared with non-surgical animals. These changes correlated with an inhibition of hippocampal neurogenesis evidenced by a decreased number of new neurons, G4 being the most affected (mean±SD for G1-4: 66.6±24; 57.6±22.2; 21.3±3.78; 5.7±0.05, p<0.05, non-parametric ANOVA).

Conclusions: Intracranial surgery was demonstrated to induce an inflammatory reaction within the hippocampus that compromised neurogenesis and impaired normal cognitive processing. Corticectomy had a much greater effect than craniotomy alone, indicating a central trigger that resulted in distant hippocampal inflammatory changes. POCD after brain surgery may originate from a central inflammatory response resulting from remote surgical trauma to the brain parenchyma.

Brain-Machine Interface Control of a Robotic Arm for Object Grasping is Improved With Computer-Vision Based Shared Control


Introduction: Brain-machine interface neuroprosthetic arms for people with upper limb impairment are developing quickly, but could be improved through intelligent computer-vision-based assistance. Grasping and manipulating objects requires very accurate control of a prosthetic arm and hand, and is required for these limbs to eventually be used clinically. With the computer helping to stabilize the hand during grasping, the user's control would not need to be as accurate, and they would be free to concentrate on the larger goals of the arm movements.

Methods: A brain-machine interface was used to control a robotic arm to complete a subset of tasks from the Action Research Arm Test to determine 2 subjects' functional control of the arm. The task was done with and without computer-vision-based assistance. Grasping and manipulating objects requires very accurate control of a prosthetic arm and hand, and is required for these limbs to eventually be used clinically. With the computer helping to stabilize the hand during grasping, the user's control would not need to be as accurate, and they would be free to concentrate on the larger goals of the arm movements.

Results: Both subjects successfully completed the tasks more often with the grasp assistance than without. The assistance lowered the speed with which the arm moved while near the objects, but did not increase the amount of time required to complete the task. This shows that the assistance made the movements both more accurate and more efficient. Both subjects reported that the arm was easier to use with assistance.

(Continued on Page 6)
CNS Presentations (Continued from Page 4)

ICU Versus Ward Management of Post-operative Microvascular Decompression. Lawrence J, Sekula RF, Johnson SA.


Legal Liability Associated with Elective Spine Surgery. Agarwal N, Choi PA, Hansberry CDR.


Does Longer Operative Time Translate to Increased Tumor Volume Resection in Brain Tumors? Raskin JS, Liu J, Ozpinar A, Fieseriu M, Raslan A.


Trans Osseous Cerebrospinal Fluid Fistula 14 Years after Chiari Decompression - Presentation and Management. Salvetti D, Gandhoke GS, Hauptman J, Weiner GM, Panigrahy A, Yilmaz S, Pollack IF.

Update on Surgical Management of Intracranial Hemorrhage Associated with Sinus Thrombosis. Johnson SA.

Use of External Ventricular Drainage to Reduce the Frequency of Wound Complications in Myelomeningoceole Closure. Lee PS, Greene S, Foster K.


Prophylactic Antiepileptic Medications Do Not Reduce Seizure Incidence Following Subarachnoid Hemorrhage. Panczykowski D, Jankowitz B, Ducruet A.


CNS Meeting Abstracts (Continued from Page 5)

Conclusion: By integrating brain-machine interface-based high-level control with computer-vision-based low-level control of a robotic arm, people with tetraplegia showed improved functional use of the arm. This result highlights the importance of combining neuroscience- and robotic-based assistive technologies to create a highly flexible and effective neuroprosthetic arm for people with upper limb impairment.

A Cost-effectiveness Comparison Between Open Transforaminal and Minimally Invasive Lateral Lumbar Interbody Fusions Using the Incremental Cost-effectiveness Ratio at 2-Year Follow-up Gandhoke GS, Shin HM, Chang YF, Tempel ZJ, Okonkwo DO, Gerszten PC, Kanter AS

Background & Objective: We compared health care costs associated with open transforaminal lumbar interbody fusion (TLIF) and minimally invasive lateral lumbar interbody fusion (LLIF) by calculating the incremental cost-effectiveness ratio (ICER). Thresholds for Minimum Clinically Important Difference and Minimum Cost Effective Difference for patient-reported outcome measures at 2-year follow-up were calculated.

Methods: Forty-five patients who underwent single level TLIF and 29 patients who underwent single level stand-alone LLIF were included. All costs from diagnosis through 2-year postsurgical follow up were available from a comprehensive single center data bank within a unified hospital system. Payment provided for all spine-related medical resource use from the time of diagnosis through 2 years was recorded. A 0% discount rate was applied for this economic evaluation. QALy were calculated from EQ5D collected in an unbiased manner. Difference in total cost per QALy gained for LLIF minus that for TLIF was assessed as the estimate of the incremental cost-effectiveness ratio ICER from a United States perspective.

Results: Significant improvements were observed at 2-year follow up for both TLIF and LLIF utilizing SF36PCS, ODI, VAS BP, VAS LP and EQ5D. ICER calculations revealed similar mean cumulative QALYs gained at the 2-year interval (0.67 for TLIF and 0.60 for LLIF; p=0.331). Median total cost of care following TLIF and LLIF were $44,068 and $45,574, respectively; (p=0.960). MCED thresholds with an anchor of <$50,000/QALY were higher than MCID thresholds for all patient-reported outcome measures. Total mean cost and EQSD were statistically equivalent between the 2 treatment groups.

Conclusions: Transforaminal lumbar interbody fusion (TLIF) and lateral lumbar interbody fusion (LLIF) produced equivalent 2-year patient outcomes at an equivalent cost effectiveness profile.
News & Notes

Pollack Named Distinguished Professor

Ian Pollack, MD, has been appointed to the faculty rank of Distinguished Professor at the University of Pittsburgh. This appointment honors extraordinary, internationally recognized scholarly attainment and constitutes the highest honor the university can accord a member of the professoriate.

UPMC to Install New Gamma Knife Icon

UPMC has announced plans to install the latest Gamma Knife® technology, the Leksell Gamma Knife Icon, becoming the first center in the United States to install this stereotactic radiosurgery device.

UPMC has been a North American pioneer in brain radiosurgery since it installed the first Gamma Knife in the United States in 1987. Currently, UPMC performs more than 600 Gamma Knife procedures per year, and is a major education center for Gamma Knife technologies, having trained more than 1,700 professionals from around the world over the past 20 years. The UPMC treatment team consists of professionals from neurosurgery, radiation oncology, and medical physics.

L. Dade Lunsford, MD, director of the UPMC Center for Image-Guided Neurosurgery, oversees the Gamma Knife program at UPMC Presbyterian.

The new device facilitates both rigid and mask cranial fixation systems and increases the range of options for patients who are candidates for Gamma Knife radiosurgery. The Icon model — tentatively scheduled for installation in fall 2016 — will replace the 4C model currently in service.

Gerszten, Lunsford Edit Books

Peter C. Gerszten, MD, MPH, is co-editor of the second edition textbook, Spine Radiosurgery, a comprehensive look into the latest devices, treatment planning techniques, target definition, and patient selection process in the field of spine radiosurgery.

The book’s publisher, Thieme, says the book offers “six new chapters on such topics as histopathological examination of spinal lesions, minimally invasive techniques, and treatment of spinal chordomas; more than 100 full-color illustrations; and a discussion of new treatments for metastatic spine disease and spinal cord compression.”

Samuel Ryu, MD, of Stony Brook University Cancer Center in New York, is co-editor.

L. Dade Lunsford, MD, is co-editor of the newly released book, Intracranial Stereotactic Radiosurgery, a 304-page look into this highly precise brain treatment technique.

According to the publisher, Thieme, the book lays the foundation for understanding the differentiations in various types of stereotactic radiosurgery technologies, and examines “radiosurgical procedures for a wide range of intracranial conditions/diseases including arteriovenous malformations, meningiomas, pituitary adenomas, trigeminal neuralgia, obsessive-compulsive disorder, epilepsy, ocular disorders, pediatric brain tumors, and gliomas.”

Jason Sheehan, MD, of the Gamma Knife Center at the University of Virginia, is co-editor.

Congratulations

Avniel Ghuman, PhD, was awarded the Biobehavioral Research Award for Innovative New Scientists (BRAINS) from the National Institute of Mental Health.

Nital Agarwal, MD, was appointed to the American Association of Neurological Surgeons Young Neurosurgeons Committee.

Sabrina Yancey, Gamma Knife processing technician, received the UPMC Award for Commitment and Excellence in Service (ACES).

Special Lectures and Appearances

Paul A. Gardner, MD, was a special lecturer at the Gruppo Otologico Skull Base Surgery Course in Piacenza, Italy on July 21, and together with Dr. Carl Snyderman, taught an Endonasal Endoscopic Hands-On Skull Base Cadaver Dissection Course at the 2nd National Yang-Ming University & Taipei Veterans General Hospital in Taipei, Taiwan, from July 27-29.

L. Dade Lunsford, MD, was a visiting professor — and the first William Coxe Lecturer — at Washington University in St Louis on September 11.

In the News

Joseph C. Maroon, MD, was featured in the fall 2015 issue of Indiana University Alumni Magazine. The article reviewed Dr. Maroon’s life in sports and his dedication to improving the management of sports-related concussions.

David O. Okonkwo, MD, PhD, was featured in a September 2015 Discover Magazine feature article that discussed how high-definition fiber-tracking helps doctors treat traumatic brain injury patients.

R. Mark Richardson, MD, PhD, was noted in a Pittsburgh Tribune-Review article, August 1, that featured one of his epilepsy patients treated with the new RNS Neurostimulator, an implantable device designed to help halt oncoming seizures. (Please see related article on Page 1 of this newsletter.)
RNS Offers New Hope (Continued from Page 1)

Once a week, they are asked to upload the data stored on their remote monitor to a secure website database where their treating physicians can review it and determine what changes should be made to detection or stimulation parameters to optimize seizure control.

In clinical trials, more than half of the patients treated with RNS had 50% or fewer seizures compared to their presurgical baseline. The median decrease in seizure frequency with treatment was 44% at 1 year, 53% at 2 years, and 60% or more in years 3 through 6. Since we began offering RNS at UPMC in January 2015, we have seen similar results in our patients. Importantly, this therapeutic modality returns to patients some degree of control over their disease, which we hope results in a significant improvement in their quality of life. Lastly, the ability to study chronic recordings in the epileptic brain, including responses to activity-triggered electrical stimulation, offers tremendous potential to further develop our understanding of the electrophysiological correlates of epilepsy and its treatment.

Figure 2. An RNS patient is shown how to download her brain recordings to a laptop computer.

(Please also see related article on first patient to receive the RNS implant, “McCandless woman 1st in region with implant aimed at halting seizures,” in the August 1 edition of the Pittsburgh Tribune Review at triblive.com. Video is also available on the triblive site.)