University Hospitals
Case Medical Center
Cleveland | Ohio

Volume 6 • Number 1 • Summer 2013

UH Neurological Institute Journal

SPECIAL ISSUE

A collection of presentations from a conference honoring **Dr. Anthony J. Furlan**

FREE Online CME Credit Hours • See back cover for details.

UH Neurological Institute Journal

FROM THE EDITOR

Dear Colleague,

I am pleased to bring you the Summer 2013 issue of the UH Neurological Institute Journal.

Through continuing collaboration with scientists at Case Western Reserve University School of Medicine, physicians at UH Neurological Institute test and refine the latest advances in treatment for patients with disabling neurological disorders. The Journal highlights these advances and demonstrates our interdisciplinary strengths. As an added benefit for our readers, CME credit is available for the busy practitioner interested in receiving *AMA PRA Category 1 Credits*™.

On the heels of the success of our previous issue that showcased the proceedings of a conference honoring one of our colleagues, we bring you a second special issue of abstracts from a recent conference, this time as a tribute to Anthony J. Furlan, MD, our Co-Director of UH Neurological Institute; the Chairman of the Department of Neurology at University Hospitals Case Medical Center and Case Western Reserve University School of Medicine; Gilbert W. Humphrey Professor and Chair, Case Western Reserve University School of Medicine; and a leader in state-of-the-art stroke care and research. Stroke is the fourth leading cause of death in the United States and the leading cause of disability. However, over the past 20 years, there has been nothing short of a revolution in the diagnosis and management of stroke. For the 10th Annual Cleveland Neurocritical Care & Stroke Conference in March 2013, many of the internationally renowned experts who have led this revolution gathered. To begin this special issue of the Journal, we present a series of abstracts from these experts who presented their own contributions to stroke care, much of it inspired by the work of Dr. Furlan.

As a bonus, this special issue also features the research endeavors of our medical residents from neurology, neurological surgery and psychiatry who presented posters as part of the 2013 Neurosciences Residents Research Day at UH Case Medical Center. Abstracts based on those posters are included in this issue.

For this issue, I invited conference hosts Michael DeGeorgia, MD, and Mark Walker, MD, to serve as Guest Editors. We are grateful for their assistance in producing the UH Neurological Institute Journal, and we are happy to be a part of the tribute to Dr. Furlan.

Nicholas C. Bambakidis, MD
Editor-in-Chief
216-844-8758
Nicholas.Bambakidis2@UHhospitals.org

Neurological Institute Physician Advice Line
216-844-1001

Appointment Request Line
216-844-2724

UHhospitals.org/Neuro

University Hospitals Neurological Institute

Recognized by U.S.News & World Report as one of the nation's finest neuroscience programs, University Hospitals Neurological Institute delivers innovative, integrated and individualized care to patients with diseases affecting the nervous system.

Our multidisciplinary team of neurosurgeons and neurological specialists provides a full spectrum of services, including diagnosis and treatment of brain tumors, epilepsy, strokes, spine and pain disorders, Parkinson disease, Alzheimer disease and more. Nationally recognized experts in neurology, neurosurgery, neuroradiology and other specialties collaborate to devise personalized care plans using the latest clinical advances and leading-edge technologies through our 15 Centers of Excellence:

- Brain Health & Memory Center
- Brain Tumor & Neuro-Oncology Center
- Community Neurology Center
- Comprehensive Stroke Center
- Epilepsy Center
- Functional & Restorative Neurosurgery Center
- Movement Disorders Center
- Music & Medicine Center
- Neurocritical Care Center
- Neurological & Behavioral Outcomes Center
- Neuromuscular Center
- Neuropsychiatry Center
- Neuroscience Nursing Practice Center
- Rainbow Neurosciences Center
- Spinal Neurosurgery Center

BEST HOSPITALS U.S.News & WORLD REPORT NATIONAL NEUROLOGY & NEUROSURGERY 2012-13

On the cover: *Middle cerebral artery occlusion treated with intra-arterial thrombolysis. Read more about this topic in the abstract by Joseph P. Broderick, MD, on page 18. (Illustration by Ravin Art & Design.)*

Kim Duvall, *Editorial Manager*
Bryan Kokish, *Marketing Manager*
Susan Miazga, *Senior Graphic Designer*

Volume 6 • Number 1 • Summer 2013

TABLE OF CONTENTS

ACKNOWLEDGEMENTS

For the support of the 10th Annual Cleveland Neurocritical Care & Stroke Conference and the 2013 Neurosciences Residents Research Day at UH Case Medical Center, we gratefully acknowledge the Evenor Armington Fund of UH Case Medical Center, the Mt. Sinai Health Care Foundation, and educational grants from Boehringer Ingelheim Pharmaceuticals, Inc., Integra LifeSciences, and Stryker Neurovascular. We also thank Dr. John Leigh for his commitment to this issue.

University Hospitals Case Medical Center

SCHOOL OF MEDICINE CASE WESTERN RESERVE UNIVERSITY

The commitment to exceptional patient care begins with revolutionary discovery. University Hospitals Case Medical Center is the primary affiliate of Case Western Reserve University School of Medicine, a national leader in medical research and education and consistently ranked among the top research medical schools in the country by U.S.News & World Report. Through their faculty appointments at the Case Western Reserve University School of Medicine, physicians at UH Case Medical Center are advancing medical care through innovative research and discovery that bring the latest treatment options to patients.

EDITORIAL BOARD

Foreword

Author

Werner Hacke, MD, PhD
University of Heidelberg
Heidelberg, Germany

It is a pleasure to provide the foreword to this issue of the University Hospitals Neurological Institute Journal – a special issue in honor of **Anthony J. Furlan, MD**, who has been a colleague and friend of mine for more than 20 years. I've collaborated with him on many research projects and trials aimed at the treatment of stroke. During his career, Dr. Furlan has not only made significant research contributions to our field but has promoted the careers of young investigators, many of whom contributed to this conference in his honor. At national and international levels, he has influenced the direction of trials of new therapies for stroke research with many publications. He has provided a valuable service for practicing clinicians by interpreting the results of large clinical trials, making the findings accessible and pertinent to the everyday care of his patients.

But the respect that he has won in the stroke community and in the field of neurology extends beyond his research contributions. All of those who know him well appreciate his candor, his humanity, and his generosity in supporting colleagues and trainees. We extend our congratulations to Dr. Furlan and look forward to working with him in the future. On a personal level, I am glad to know that friendship can last more than 25 years in this competitive field.

From left to right: Joseph Broderick, Cathy Sila, Alex Abou-Chebl, Lawrence Wechsler, Nancy Futrell, Judith Hinchey, Richard Jung, Louis Caplan, J.P. Mohr, Anthony Furlan, Marc Chimowitz, Marc Fisher, Derk Krieger, Michael DeGeorgia, Werner Hacke, Aasef Shaikh, Jennifer Sweet, Randall Edgell, Ashish Nanda, Irene Katzan, Richard Leigh and Marilou Ching.

Stroke Diagnosis and Management in the 21st Century: AJ Furlan and a Glimpse of Canaan

Author

JP Mohr, MD
Columbia Presbyterian Medical Center
New York, New York

Much has changed since the start of the careers of our host and the current speaker. In 1974, when Dr. Furlan's first literature contribution appeared, he was concerned with subacute sclerosing panencephalitis and multiple sclerosis – not stroke – but it did not take long for him to see the light at the end of the tunnel, only to discover an approaching train. In the four decades since awakening to his calling, he steered straight into some of the major controversies in diagnosis and management.

Dr. Furlan's early studies focused on clinical hints for diagnosis, such as unilateral visual loss to bright light as a sign of critical carotid stenosis. His forays into epidemiology during his fellowship at the Mayo Clinic led to the correct observation of the decreasing incidence of intracerebral hemorrhage. Many are happy that an experience with a frozen commode in a rental home in Rochester is among the reasons that prompted a move to Cleveland. Not long after his arrival in Cleveland, Dr. Furlan began a long trek to improve stroke therapy. Involved in the introduction of innovations in thrombotic therapy, he was among those documenting the hazards to some treatments that many had hoped would be beneficial. He also played a major role in assessing the emergence of interventional devices for clot extraction. He has been prominent among the hearty group that has done the heavy lifting for setting standards for clinical performance. His center contributed 32 patients to WARSS, a large multicenter trial comparing two classes of antithrombotic therapy. He shared the consternation when the expected major difference in recurrent stroke rates for the two therapies failed to be shown. One of the substudies of that trial was the assessment of patent cardiac foramen ovale and a mechanism for recurrent stroke – little impact was shown on recurrence rates. A similar lack of major differences occurred in a subset of patients with predominantly intracranial large artery disease of intracranial atherosclerosis. Efforts to improve outcomes with endovascular angioplasty and stenting demonstrated frequent adverse events, forcing a premature end to the trial. These results were similar to a subsequent trial with a larger cohort. Similar disappointments have been found in extracranial to intracranial bypass. Intravenous and intra-arterial tissue plasminogen activator and attempts to extract the clot may not yield the outcomes that were hoped for. But this is not the end of the story. Means will be found to generate prompt correlations across borders to spare infarction in the tissue at risk. One subject seems close to being settled – closure of a patent cardiac foramen ovale. Dr. Furlan has been the point man for controversies around closure of a patent cardiac foramen ovale by leading the large CLOSURE trial. The results from the PICSS substudy from WARSS looked as though a difference in ischemic stroke recurrence might be difficult to show. No stranger to design issues, Dr. Furlan offered the best opportunity for closure of an endovascular patent foramen ovale by including transient ischemic attacks, hoping to increase the observable event rates to a statistically significant level. The study used CardioSEAL (Nitinol Medical Technologies, Boston, MA) and took more than seven years for its completion. During this time, the trial faced numerous

challenges. Many internationalists bypassed the trial by using other devices that were mainly designed for ventricular (not atrial septal) defect closures. Action by the FDA blunted these "compassionate use" options, but the trial slowly accumulated its cases and stopped when about 900 cases had been randomized. The results, presented by Dr. Furlan at the American Heart Association meeting in Chicago in 2010, have tempered the enthusiasm for referral for closure of a patent foramen ovale. Eager for an outcome for presentation to the FDA, the sponsoring company was keenly disappointed with the final results and is now out of business. Our host continues to dismiss efforts to trivialize the results of the trial. The hopes for a more favorable outcome for the most recent competing trial (RESPECT), using the Amplatzer (AGA Medical Corporation, Golden Valley, MN) device, were not met by the results, which demonstrated less device-related atrial fibrillation but no statistically significant difference in outcome. It has been more than a century since the synthesis of aspirin, the active agent in the tree bark that Native Americans used as a broth to cure illnesses. It has been almost 70 years since the discovery and synthesis of warfarin, the active agent in rotten clover that causes hemorrhage in dairy cows. These two forms of therapy continue to this day. Both are under challenge from newer agents with slightly different mechanisms of action. One can only ask if they will still be fending off challenges at the end of this century or be remembered only by those interested in the history of stroke diagnosis and therapy. Whatever happens, a portrait of our host on the wall near departmental offices will serve as an inspiration to those seeking a model for career development.

Dr. Mohr reports no financial relationship with a commercial interest relevant to this abstract.

Carotid Endarterectomy: Which Patients Benefit Most?

Author

Lawrence R. Wechsler, MD
University of Pittsburgh School of Medicine
Pittsburgh, Pennsylvania

Carotid endarterectomy (CEA) for carotid stenosis dates to the 1950s and became increasingly utilized over the next few decades. Appropriate indications for CEA were unclear until randomized clinical trials beginning in the 1980s and 1990s clarified the role of CEA in symptomatic and asymptomatic stenosis. The North American Symptomatic Carotid Endarterectomy Trial randomized patients with 30 – 99% stenosis to either surgery or medical therapy with 1300 mg of aspirin daily. In 1991, initial results demonstrated a significant reduction of stroke and death in patients with 70 – 99% stenosis and no benefit for those with less than 50% stenosis. Similar results from the European Carotid Surgery trial were reported. After several additional years of follow-up, both studies reported a significant but lesser benefit for patients with moderate degrees of stenosis in the 50 – 79% range. Subgroup analysis suggested that men benefited more than women, patients with hemispheric transient ischemic attacks benefited more than those with retinal symptoms, and older patients benefited more than younger patients. The reduction in stroke events was greatest for those operated on within two weeks of symptoms. The Asymptomatic Carotid Atherosclerosis Study and Asymptomatic Carotid Surgery Trial randomized asymptomatic patients with at least 60% stenosis to surgery or medical therapy. Both studies demonstrated a reduction in stroke and death with CEA, but the absolute benefit was small. Although surgical results have improved, advances in medical therapy since these studies were performed raise questions regarding the applicability of the results of these studies to current patients and suggest that new studies comparing surgery and medical therapy are necessary.

Dr. Wechsler has stock options in Neuro Interventional Therapeutic and Silk Road, and the CME Program has determined there is no conflict of interest.

Extracranial Stenting: Which Patients and When

Author

Randall C. Edgell, MD
University of Texas Health Science Center
Houston, Texas

The carotid bulb is the most frequent site of large artery atherosclerotic stenosis associated with stroke and has been studied in great detail. Atherosclerotic disease of the vertebral artery origin is likely the second most common site, but the study of this disorder is at an early stage.

Our understanding of which patients are at high risk for carotid endarterectomy (CEA) has evolved since the first attempts to define this group and the publication of the CAVATAS and SAPPHIRE trials. While some assumptions such as the higher risk of myocardial infarction with CEA have been confirmed, others such as increased operative risk relative to carotid artery stenting (CAS) with increasing age have not. Modifications of the high-risk patient population are discussed in light of the Carotid Revascularization Endarterectomy versus Stent Trial (CREST) results.

Vertebral artery origin stenosis, while long recognized as prevalent in the stroke population, is lacking an evidence base upon which to make treatment recommendations. The multicenter vertebral artery origin stenting registry for the Society for Vascular and Interventional Neurology has confirmed the low risk of stenting at this location. However, there is a pressing need to build on the natural history study performed by Dr. Furlan and colleagues in the 1980s in order to determine the risk of recurrent stroke in the medically managed patients with vertebral artery origin stenosis.

Carotid artery stenosis and vertebral artery stenosis, while similar in prevalence in the stroke population, have had diverging emphasis in the stroke research community. Although the treatment of carotid stenosis can now be tailored based on extensive data, vertebral artery origin stenosis is still in need of a prospective study to elucidate the natural history and best treatment options.

Dr. Edgell reports no financial relationship with a commercial interest relevant to this abstract. This abstract includes discussion of unlabeled/investigational uses of a commercial product.

EC-IC Bypass: History, Facts, and Controversies

Author

Nancy Futrell, MD
Intermountain Stroke Center
Salt Lake City, Utah

Extracranial to intracranial (EC-IC) bypass surgery was frequently performed in the 1970s and 1980s to prevent stroke in patients with carotid occlusion or severe carotid stenosis. When the initial trial was published in 1985, the procedure was shown to be ineffective at preventing stroke. Subsequent publications clarified that the EC-IC bypass did not necessarily result in increased blood flow to the territory of the ipsilateral middle cerebral artery. It is also clear that EC-IC bypass did nothing to remove sources of embolism in the internal or external carotid arteries – in fact they could have provided a new conduit for embolism from the external carotid artery.

The trial was criticized by Thor Sundt, who questioned the applicability of the results of the trial to individual patients. Other reports delineated strategies to improve patient selection by using perfusion testing with acetazolamide challenge or positron emission tomography to find patients with hypoperfusion ipsilateral to severe carotid disease. This strategy culminated in a study by William Powers, published in the Journal of the American Medical Association in 2011, that again was unable to show a benefit of EC-IC bypass.

Dr. Louis Caplan discusses the need for evaluating individual patients rather than using evidence-based medicine for all clinical decisions. The EC-IC bypass is a surgical procedure that requires this individualized approach.

Two patients will be presented that demonstrate utility of the procedure on an individual basis. The number of patients who will benefit from EC-IC bypass is small. Given the small number of surgeries being performed, the number of qualified surgeons is small. Centers of excellence for EC-IC bypass should be maintained to provide this procedure for carefully selected patients. Databases should be maintained to improve patient selection.

Dr. Futrell reports no financial relationship with a commercial interest relevant to this abstract.

What's Next in the Treatment of Atherosclerotic Intracranial Stenosis: Lessons Learned from SAMMPRIS

Author

Marc I. Chimowitz, MBChB
Medical University of South Carolina
Charleston, South Carolina

Intracranial atherosclerotic stenosis of a major intracranial artery is one of the most common causes of ischemic stroke, especially in African-Americans, Asians and Hispanics. It is associated with a particularly high risk of recurrent stroke. Clinical trials over the past decade have suggested roles for dual antiplatelet therapy, intensive management of risk factors and endovascular therapy, but until recently these treatments had not been compared head-to-head.

The early results of the ongoing Stenting and Aggressive Medical Management for Preventing Recurrent stroke in Intracranial Stenosis (SAMMPRIS) trial showed that aggressive medical management (aspirin 325 mg daily and clopidogrel 75 mg daily for 90 days followed by aspirin alone, intensive management of risk factors, and a lifestyle program) is superior to angioplasty and stenting with the Wingspan stent system plus aggressive medical management because of the high risk of early stroke after stenting and lower than expected risk of stroke on aggressive medical therapy alone. Compared with patients treated with usual medical management in the Warfarin Aspirin Symptomatic Intracranial Disease (WASID) trial, patients treated with aggressive medical management in the SAMMPRIS trial had a much lower rate of any stroke or death within 30 days of enrollment or stroke in the territory beyond 30 days (12.2% at one year in SAMMPRIS vs. 25% at one year in WASID). Nevertheless, the one-year rate in the SAMMPRIS trial indicates that there are still subgroups of patients who are at high risk of stroke despite aggressive medical therapy.

Future research is needed to identify high-risk patients reliably and to develop more effective treatments for these patients. Noninvasive vascular imaging that could identify high-risk patients include quantitative magnetic resonance angiography and magnetic resonance imaging (MRI) or computed tomography perfusion to identify impaired flow distal to a stenosis as well as high resolution MRI of atherosclerotic plaque to identify high-risk features, such as intraplaque hemorrhage, large lipid core, and ruptured fibrous cap. Secondary preventive therapies that may be considered for future clinical trials include angioplasty alone, indirect revascularization techniques, ischemic preconditioning, and direct thrombin or Xa inhibitors.

Dr. Chimowitz has received research support from Stryker Corporation and AstraZeneca, and the CME Program has determined there is no conflict of interest.

Angioplasty and Stenting for Intracranial Stenosis: The View from the Cath Lab

Author

Alex Abou-Chebl, MD
University of Louisville
Louisville, Kentucky

Intracranial atherosclerosis is a major cause of stroke, and its natural history is poorly understood. Even with medical therapy, the stroke risk remains high, mandating better solutions. Surgical revascularization is associated with an increased stroke risk compared to rudimentary (by current standards) medical therapy, leaving percutaneous angioplasty and stenting (PTAS) as the current therapeutic alternatives. Although small series have shown promising results over the years, the SAMMPRIS trial showed that medical patients fared better in the first 30 days than PTAS patients. The SAMMPRIS trial – the largest randomized trial of medical vs. PTAS therapy – was stopped early as a result, and the long-term results have yet to be presented. As a consequence, PTAS has fallen out of favor in the eyes of many clinicians. However, the SAMMPRIS trial results cannot be interpreted as disproving the efficacy of PTAS as a whole. Though well-conducted, the trial had flaws, particularly in the procedure and patient selection that biased the results toward medical therapy. Current best practice should take into account individual patient factors, such as the presence of abnormal cerebrovascular reserve or hemodynamically significant lesions, which may indicate a subset of patients most likely to benefit from PTAS. Lesion details such as small vessel size, eccentricity and lesion length indicate patients who are at a high risk of complications; PTAS may be contraindicated for these patients. Patients who present with perforator syndromes are unlikely to benefit and should not be treated with PTAS or enrolled in trials of PTAS because they have a different disease than the patient who presents with large vessel ischemia distal to the stenosis. These procedures should be performed under local rather than general anesthesia to decrease the risk of complications. Importantly, physicians performing these procedures need to have extensive experience treating atherosclerotic intracranial disease; experience using self-expanding stents for aneurysm reconstruction is not sufficient. When performed properly and in appropriate patients, PTAS can be performed safely. It remains a reasonable alternative for patients who fail maximal medical therapy. Further research is warranted.

Dr. Abou-Chebl has received honoraria from Codman, and the CME Program has determined there is no conflict of interest. This abstract includes discussion of unlabeled/investigational uses of a commercial product.

The Heart-Brain Connection Rekindled:
Innovative Screening for Atrial Fibrillation after Stroke

Author

Derk W. Krieger, MD, PhD
University of Copenhagen
Copenhagen, Denmark

Atrial fibrillation (AF) is responsible for approximately 20% of all ischemic strokes. Overall, AF increases risk of stroke five-fold, and AF-related strokes are more likely to be fatal than non-AF-related strokes. Finding paroxysmal AF in patients after stroke diminishes cryptogenic stroke and increases the number of patients requiring anticoagulation. Currently, most stroke patients with AF are offered anticoagulation, preferably novel oral anticoagulants. The benefit of preventive anticoagulation is only shown to be beneficial in patients with stroke and ongoing or prior AF. It is not known whether patients with cryptogenic stroke found to have AF during long-term monitoring have the same risk. These patients are often older than those previously enrolled into the pivotal anticoagulation trials and, because their burden of AF can be quite small, their future stroke risk may be different. It is undetermined which duration of AF episode or daily burden of AF increases stroke risk. AF may also be found in patients with other stroke subtypes and risk factors. Successive strokes may have different causations in the same patient. In all prior anticoagulation trials, ischemic stroke or systemic thromboembolism served as the clinical efficacy endpoint. Stroke subtypes have never been included in these assessments, but doing so may become necessary to sustain the level of stroke risk reduction when prescribing anticoagulants in these individuals. In contrast, the index stroke may be such a powerful indicator that no further attributes are required. Future research will determine the need for oral anticoagulants in this novel patient population.

Dr. Krieger receives research support from Medtronic and is a speaker for Medtronic and Boehringer-Ingelheim, and the CME Program has determined there is no conflict of interest.

Anticoagulation for Atrial Fibrillation:
Current Strategies

Author

Marilou Ching, MD
University of Buffalo,
State University of New York
Buffalo, New York

Atrial fibrillation (AF) is a common sustained cardiac arrhythmia. Its prevalence increases with age, affecting more than 10% of patients greater than 80 years old. By far the most serious common complication of AF is arterial thromboembolism, and the most clinically evident embolic event is ischemic stroke. The rate of stroke among patients with AF varies between 1% and 20% annually. Anticoagulation with Vitamin K antagonist has been shown to lower the risk of clinical thromboembolism in virtually all patients with AF, irrespective of type (paroxysmal, persistent or permanent).

For the past 60 years, warfarin has been widely prescribed. However, its impact in preventing thromboemblism is hampered by limitations based on its side effect profile as well as patient-related issues of adherence and convenience. Since 2010, newer oral anticoagulants have gained approval in many countries including the United States. Dabigatran is a direct thrombin inhibitor approved by the FDA in October 2010 for the prevention of stroke or systemic embolism in adult patients with nonvalvular AF and at least one risk factor for stroke. In a trial of dabigatran versus warfarin in patients with AF, dabigatran at a dose of 110 mg twice a day was associated with rates of stroke and systemic embolism comparable to warfarin. The rate of major hemorrhage was less. On the contrary, 150 mg of dabigatran twice a day was associated with lower rates of stroke and systemic embolism but similar rates of major hemorrhage. Two oral anticoagulants that are selective for Factor Xa in the prevention of nonvalvular AF are rivaroxaban and apixaban. In the ROCKET AF trial, rivaroxaban was superior to warfarin in preventing stroke or systemic embolism. There was no significant difference between groups in the risk of major bleeding, although intracranial and fatal bleeding occurred less frequently in the rivaroxaban group. In the ARISTOTLE trial, apixaban was superior to warfarin in preventing stroke or systemic embolism, caused less bleeding, and resulted in lower mortality. It is important to acknowledge that there are several unresolved issues related to the use of these novel oral anticoagulants. While these agents are convenient for patients such that coagulation monitoring is not necessary, challenges exist until methods to monitor drug levels and antidotes are developed. Moreover, results of the trials are based on limited duration of follow-up. Lastly, it remains unknown whether patients on these agents are safe to receive intravenous thrombolytics. Until more data exist, the use of these agents should be individualized with consideration of its risk-benefit ratio.

Dr. Ching reports no financial relationship with a commercial interest relevant to this abstract.

Imaging Selection of Stroke Patients for Acute Therapy

Author

Marc Fisher, MD
University of Massachusetts Medical School
Worcester, Massachusetts

Therapy of acute ischemic stroke early after onset with intravenous (IV) tissue plasminogen activator (tPA) has been shown to be beneficial. This clinical benefit presumably reflects partial salvage of ischemic tissue amenable to treatment (i.e., the ischemic penumbra by thrombolysis induced reperfusion). As time passes after stroke onset, the ischemic penumbra shrinks and more of the ischemic region becomes irreversibly injured. It is obvious that the target of acute stroke therapy is to salvage as much of the penumbra as possible to improve functional outcome. Advanced imaging techniques, especially diffusion-weighted and perfusion-weighted MRI (DWI/PWI), provide the opportunity to view the ischemic penumbra in real time and to potentially identify patients more or less likely to respond to various therapeutic modalities. Two DEFUSE studies provide data that both IV tPA up to six hours from stroke onset and endovascular therapy up to eight hours from onset are associated with improved outcome in patients who have a target DWI/PWI mismatch, the MRI signature of the ischemic penumbra. The EPIETHET trial also suggested benefit for IV tPA up to six hours from stroke onset in patients with a DWI/PWI mismatch. The recent demonstration of enhanced recanalization efficacy with the Solitaire (Ev3, Plymouth, MN) and Trevo (Stryker Corporation, Kalamazoo, MI), stent retrievers for clot removal suggests that the use of these endovascular devices in late time-window stroke patients who have MRI evidence of an extensive ischemic penumbra is likely to be associated with significant improvement in outcome.

Dr. Fisher reports no financial relationship with a commercial interest relevant to abstract.

Advances in MRI-Guided Treatment of Acute Stroke Patients

Author

Richard Leigh, MD
The Johns Hopkins Hospital
Baltimore, Maryland

The treatment of acute ischemic stroke (AIS) was launched more than a decade ago with the approval of intravenous (IV) tissue plasminogen activator (tPA) for use in a subset of patients. However, the use of IV tPA has been restricted to patients who can be treated very soon after the onset of symptoms, resulting in only a small portion of AIS patients receiving treatment. This time-window based approach to patient selection ignores the heterogeneity of stroke patients and stroke mechanisms. Even in approved time windows, the use of IV tPA can result in the most feared complication of stroke treatment – symptomatic intracranial hemorrhage – in approximately 6% of AIS patients. Traditionally, MRI has not played a role in the selection of AIS patients for IV tPA. However, MRI is capable of providing detailed information about the pathophysiology of AIS. It is the goal of our research to develop ways to use MRI to increase the number of patients who can be safely treated with IV tPA while minimizing the complications associated with treatment. Our approach to reaching this goal has three components: 1) better use of the information we are currently acquiring with MRI through quantification; 2) extracting novel information out of the standard images through post-processing; and 3) developing new ways to acquire images that are targeted to specific physiologic and pathologic processes. To address the first component, we have developed an image processing pipeline that allows real-time quantification and volumetric analysis of MRI. The focus of the second component has been on developing a method for measuring damage to the blood-brain barrier from perfusion-weighted source images. Lesions on blood-brain permeability imaging have been shown to be independent predictors of intracranial hemorrhage after IV tPA. For component three, we are testing a novel pulse-sequence that generates pH-weighted images. This imaging was developed to detect the build-up of lactic acid in the brain that occurs in the setting of poor blood flow and has the potential to identify at-risk (penumbral) tissue.

Dr. Leigh reports no financial relationship with a commercial interest relevant to this abstract.

Intra-arterial Thrombolysis and Thrombectomy

Author

Ashish Nanda, MD
University of Missouri School of Medicine
Columbia, Missouri

Stroke is the fourth leading cause of death in the United States, with about 795,000 new strokes each year resulting in more than 200,000 deaths per year in the United States. In addition to intravenous (IV) tissue plasminogen activator (tPA), newer interventional treatments have emerged over the past decade to help achieve better recanalization, with goals of improved outcomes. These emerging therapies aim to reduce the burden of stroke-related morbidity and mortality and to lessen the long-term financial burden on society. Randomized controlled trials like PROACT II have demonstrated clinical efficacy for intra-arterial thrombolysis in selected patients with acute middle cerebral artery occlusion. Certain usage limitation and lower rates of recanalization from tPA led to the evolution of devices like MERCI (Concentric Medical, Mountain View, CA) and Penumbra (Penumbra, Alameda, CA), designed specifically for extracting clots from major cerebral arteries. The trials of these newer devices showed improved recanalization rates with improved outcomes in the patients where revascularization was achieved. Newer stent retrievers including Solitaire (Ev3, Plymouth, MN) and Trevo (Stryker Corporation, Kalamazoo, MI) are designed to achieve immediate flow restoration in adjunct to clot retrieval. Trials of these stent retrievers have shown even further improvement in the recanalization rates with outcome of functional independence in more than half of the intervened patients. As emerging endovascular stroke therapy was getting widely recognized, the recently published IMS-III trial showed no additional benefit of endovascular therapy in addition to IV tPA during the first three hours of stroke, thus raising questions about its use in patients eligible for IV tPA. Newer endovascular technologies have expanded the treatment options for stroke patients with catheter-based drug administration and mechanical embolectomy, leading to a promising alternative for patients who are ineligible for standard IV thrombolytic therapy. However, more randomized control trials are warranted to prove its efficacy and safety and to establish it as a standard of care in stroke patients.

Dr. Nanda reports no financial relationship with a commercial interest relevant to this abstract.

Quality of Stroke Care

Author

Irene Katzan, MD, MS
Cleveland Clinic Neurological Institute
Cleveland, Ohio

Dramatic advancements have been made in the assessment of stroke care quality over the past 10 years. Spurred on by the approval of intravenous tissue plasminogen activator for stroke and the increasing national focus on measuring quality of health care, we have changed the way we measure and define quality of care. In 2002, a voluntary national quality registry for stroke, the Get with the Guidelines – Stroke™ Patient Management Tool, was implemented. More than 1,000 hospitals are now participating in the registry, which includes more than a million patients hospitalized with stroke. Primary Stroke Center (PSC) certification was developed by The Joint Commission in December 2003. There are now almost 1,000 hospitals certified by The Joint Commission and many more certified by state regulatory bodies. The evidence for improved outcomes in PSC hospitals is limited, although the benefit for stroke units has been well-established in randomized controlled trials from the United Kingdom and Europe, and there is general consensus that a systematic approach to stroke management and the following general therapy rules is beneficial for patient care.

In 2013, eight stroke performance measures will be included in the Centers for Medicare and Medicaid Services (CMS) In-hospital Quality Reporting Initiative. For the first time, stroke measures will be publicly reported. A process for determining a Comprehensive Stroke Center has been developed, with 70 hospitals applying on the first day. A hospital tiering system that can be used to coordinate a national system for stroke care has the exciting potential to improve access to appropriate level care for stroke patients in the United States. The demands for collecting and reporting process measures for stroke and other diseases produce a strain on health care systems. The expanding availability of electronic health records (EHR) and capabilities of health information technology (HIT) will be one solution to reduce this burden for hospitals and providers. In addition, initiatives like "Meaningful Use of EHRs" which arose from the Health Information Technology for Economic and Clinical Health (HITECH) Act, will lead to improvements in functionality of EHRs that can be used to improve adherence to stroke performance measures and improve standardization of other aspects of stroke care. The ability to leverage HIT will likely be an important component of stroke quality improvement initiatives in the future. Another national trend is to measure outcomes of care in addition to process measures. For example, the CMS Value-based Purchasing Program will adjust hospital reimbursements based on selected outcome measures in 2014. Two new outcome measures for stroke were reviewed by the National Quality Forum (NQF) this past year. Although these proposed measures were not endorsed by NQF, there will likely be more outcome measures for stroke proposed in the future. The move to measure and be accountable for outcomes of care will likely result in further modifications in our approach to quality improvement initiatives related to stroke. Variables used to adjust case-mix must be rigorously collected. Hospital systems will further integrate their practices across disciplines and venues because the factors affecting stroke outcomes span the range of health care services. The landscape of stroke quality management and assessment is being transformed. The next several years are sure to be interesting and challenging and sure to provide opportunities to further optimize care of patients with stroke.

Dr. Katzan reports no financial relationship with a commercial interest relevant to this abstract.

Intravenous tPA Followed by Endovascular Thrombolysis Drip and Treatment

Author

Joseph P. Broderick, MD
University of Cincinnati Neuroscience Institute
Cincinnati, Ohio

The Interventional Management of Stroke (IMS) III trial demonstrated no difference in functional independence as measured by the modified Rankin Scale (0 – 2) and similar safety with intravenous (IV) tissue plasminogen activator (tPA) followed by endovascular therapy as compared to IV tPA alone. In the subgroup of patients with pretreatment computed tomographic angiography (about half of the study) who had occlusions of the first division of the middle cerebral artery, 24-hour recanalization rates were high and modified Rankin Scale outcomes were similar in the two treatment arms. By contrast, patients with a carotid "T" and tandem occlusions of the internal carotid artery and M1 showed greater recanalization and better outcomes with IV tPA plus endovascular treatment compared to IV tPA alone. Following an active intravenous therapy, successful endovascular reperfusion of remaining major arterial occlusive lesions was associated with improved functional outcome. Nevertheless, the majority of such subjects who reperfused still had poor functional outcomes. We found a strong relationship between time-to-reperfusion and functional independence at 90 days. Given data from reperfusion trials of myocardial infarction, the strong relationship between onset-to-needle time and effectiveness of IV tPA, and subgroup data from IMS III, future trials of endovascular therapy must minimize delays to initiation of endovascular therapy. Early thrombectomy technology applied in IMS III had more associated adverse events, which may have reduced clinical efficacy in the endovascular group compared with IV tPA therapy. Randomizing subjects in ongoing and future stroke trials, rather than treating eligible patients with endovascular therapy outside of any trial, will be essential for assessing the potential benefit of endovascular therapy. The ability of newer thrombectomy methods to improve functional outcome as compared to standard therapy with IV tPA alone remains to be demonstrated.

Dr. Broderick has received grant/research support from Genentech and Schering Plough, and the CME Program has determined there is no conflict of interest. This abstract includes discussion of unlabeled/investigational uses of a commercial product.

Still Questioning the Accuracy of Predicting in-Hospital Stroke Mortality

Author

Judith A. Hinchey, MD
Tufts Medical School
Boston, Massachusetts

For years, attempts have been made to use in-hospital stroke mortality to measure the quality of care a hospital provides. In 1986, the Health Care Financing Administration published stroke mortality rates for Medicare patients by hospital. The information was criticized because of the lack of criteria to specify the severity of illness, which is important when comparing hospitals that attract different populations of patients. Because the data was thought to be too inaccurate to be useful, the study was stopped. When I came to Cleveland, Ohio, to study under Dr. Furlan, the Cleveland Health Quality Choice coalition was overseeing a similar project. This coalition of business professionals wanted to use in-hospital mortality to compare hospitals' quality of care in order to influence corporate health plan choices. The model they used was good at predicting in-hospital death (83% concordance rate). By using level of consciousness, do-not-resuscitate status by day three, and mass effect on computed tomography scan, the model accurately predicted higher mortality rate in patients with severe strokes. It had the most difficulty predicting mortality in patients with moderately sized strokes – the patients for whom quality of care may be most important in determining outcome. We concluded that unless prediction models used more neurologic-specific variables, such models would not be able to distinguish between different severities of illness and therefore would not be presenting accurate measures of quality. The hospitals in Cleveland stopped participating, so the project was shut down.

Since then, there have been other attempts to develop stroke mortality prediction models but none is ready to be used to make decisions regarding care. No data tell us whether these mortality prediction models do what they purported to do, which is to assess the quality of care. By definition, if a mortality rate is higher than expected, then some deaths were preventable. We will not be able to determine if a death was preventable until we understand how we prevent death. Dubois and Brooks found that approximately 18% of stroke deaths were preventable. These deaths were preventable because there was inadequate diagnostic work-up, inadequate fluid management, inadequate treatment of cerebral edema, or inadequate management of sepsis that led to the death. I propose that a major factor in the prevention of death is the manipulation of cerebral perfusion. Changes in the level of the head of the patient's bed, intravenous fluid amount and blood pressure range help increase perfusion in small- to moderate-sized strokes or limit perfusion and help drainage in moderate- to severe-sized strokes. The gradations are determined based on the patient's clinical signs, symptoms, comorbidities and knowledge of vascular anatomy. This is the art of stroke care. (This specific

management is not based on clinical trials and will not be included in stroke guidelines.) Not all stroke specialists agree on the correct positioning, volume or blood pressure range for any given patient. If there is general agreement that manipulation of cerebral perfusion is one of the most important factors that determine outcome (mortality and functional outcome), how does this affect our stroke mortality prediction models? It may not be reasonable to think that every hospital in the United States will have a physician with the ability to accurately manipulate these factors such that all patients with stroke receive the correct management. Should such a hospital still be taking care of stroke patients? Should we use the mortality prediction models to prospectively identify those patients who should be cared for by others with more experience in stroke care via hospital transfer or telemedicine? We need more data. We need data regarding the care received by patients who had possibly preventable deaths. Was the death preventable and, if so, how? What are the up-to-date reasons for preventable death? We have some prediction models, but they should not be used to compare hospitals or influence patient management until we spend more time studying whether the models are assessing quality of care. Dubois and Brooks started on this track 22 years ago. It is time we got back on the correct path.

Dr. Hinchey reports no financial relationship with a commercial interest relevant to this abstract.

Translating Trials and Guidelines to the Care of Individual Patients

Author

Louis R. Caplan, MD
Harvard Medical School
Boston, Massachusetts

Neurologists and other physicians treat one patient at a time. The traditional rules for caring for patients are rather simple:

1. Find out what is wrong with the patient in as much detail as possible.
2. Understand the patient's risks for disease and for complications.
3. Learn about the patient – his or her background, genetics, stresses, socioeconomic milieu, psychology, responsibilities, goals, etc.
4. Consider all potential treatments and estimate the benefits and risks of potential therapeutic strategies to treat the patient's conditions, which are often multiple, and to prevent conditions that the patient is at risk of developing.
5. Communicate with the patient, family and friends. Listen, inform and teach.

Utopians dream that all future treatment will be based on the results of randomized therapeutic trials (so-called evidence-based medicine). The challenge is how to apply the results of therapeutic trials and guidelines to the care of complex individual patients.

Trials are very different from individual patient care. Trials require recruitment of hundreds or thousands of patients to satisfy statisticians whose hunger for numbers is insatiable. Only common conditions with readily detectable end points, such as mortality, are studied. One or several treatment strategies may be studied; all patients are treated uniformly. A lumping strategy is applied so that enough numbers are available to detect statistically significant results.

Using stroke as an example, some trials are general and some are specific. General trials may include trials of antiplatelet agents in pooled groups of heterogeneous, incompletely studied patients with transient ischemic attacks or minor strokes. Specific trials may include those that study carotid surgery and stenting, or stenting versus medical therapy.

General trials yield information about the frequency of side effects and whether the treatment is effective. These trials and the guidelines based on their results are useful for physicians who are not specialized or appropriately knowledgeable about the condition they may be treating, such as emergency room physicians and general practitioners in the treatment of stroke. In trials that are potentially useful for stroke specialists, patients are well-evaluated, stroke subtypes and cardiovascular lesions are well-defined, numbers and power are adequate, the situations and treatments studied are applicable to individual patients, and the end points chosen are realistic and clinically meaningful. The full data from these trials should be available so that clinicians can determine how well the patients studied match the patient for whom the clinician must choose treatment.

Dr. Caplan reports no financial relationship with a commercial interest relevant to this abstract.

The initial part of the conference to honor Dr. Furlan consisted of the 2013 Neurosciences Residents Research Day at University Hospitals Case Medical Center. Research Day was sponsored by Mt. Sinai Health Care Foundation, and the judges were invited speakers to the conference. The following abstracts were written by the residents from neurology, neurological surgery and psychiatry who submitted posters. CME credit is not provided for reading the resident abstracts.

Baseline Diffusion-Weighted MRI Characteristics in Patients with Cryptogenic Stroke and Patent Foramen Ovale: Results from the CLOSURE I Trial

Authors: Richard S. Jung, MD; Benny S. Kim, MD; Joseph Massaro, MD; Sammy Elmariah, MD; Shuqiong Ling, MS; Laura Mauri, MD; Anthony J. Furlan, MD

Background: We evaluate the predictive value of baseline diffusion-weighted magnetic resonance imaging (DWMRI) characteristics in patients with cryptogenic stroke or transient ischemic attack (TIA) and patent foramen ovale (PFO) from the CLOSURE I trial. Cryptogenic stroke may have several etiologies, including paradoxical embolism through a PFO. CLOSURE I compared device closure versus medical therapy for secondary prevention in patients with cryptogenic TIA or stroke and PFO with primary end point of two-year rate of stroke, TIA or cerebrovascular death.

Methods: Baseline MRI performed in 887 of 909 randomized patients were reviewed by a blinded core laboratory. Analyses were performed in the intention-to-treat population. Recurrent ischemic stroke or TIA defined primary end point and secondary end points were recurrent stroke or TIA. Multivariate proportional Cox regression compared imaging subgroups. Three cohorts were defined by MRI: no acute infarct, acute lacunar infarct and acute nonlacunar infarct. Multiplicative terms were used to test for interaction between baseline imaging and randomization group (closure vs. medical). Kaplan-Meier plots were created to assess event-free survival and between groups.

Results: 537 patients had a DW+ acute infarct on baseline MRI, and 349 had no acute lesion. 440 patients had acute nonlacunar infarcts, and 97 were acute lacunar infarcts defined as a single, DW+ subcortical infarct less than 1.5 cm. There was no significant difference in baseline MRI pattern between the device and medical arms. There was no significant difference in age or vascular risk factors or primary outcome between the three cohorts. Adjusting for baseline characteristics did not discriminate between device and medical therapy for composite primary outcome. Patients with no baseline infarct had a higher rate of TIA (HR 0.39, CI = [0.16, 0.90], P = 0.028).

Conclusion: Specificity of DWMRI infarct patterns for cardiac embolism in cryptogenic stroke and PFO is uncertain. Enrolled patients showed a variety of baseline DWMRI patterns with 62% single and 38% with multiple infarcts. Most of the infarcts involved cortical or immediate subcortical areas, but 18.5% appeared lacunar. Our analysis revealed no significant difference in baseline MRI patterns between device and medical arms, nor did it discriminate age or vascular risk factors between cohorts. The baseline imaging pattern did not identify a subgroup of patients that benefits from PFO closure within a two-year period. Patients with no acute lesion on baseline MRI had an increased risk of TIA compared with those with acute nonlacunar infarcts. Patients with acute lacunes had increased risk of stroke compared with those with no baseline infarct but not compared to nonlacunar baseline infarcts.

The Role of Cerebellum in Perception of Motion

Authors: Aasef G. Shaikh, MD; David S. Zee, MD; Dominik Straumann, MD; R. John Leigh, MD

Background: We assessed the role of cerebellum in the physiology of motion perception and implemented these concepts to describe the novel feature of cerebellar strokes affecting dorsal lobule IX that manifest as intractable vertigo but normal oculomotor function. The motion perception and the vestibuloocular reflex (VOR) have distinct functions. The VOR keeps the gaze steady on the target of interest, while perception serves the awareness of self-motion and orientation. VOR and motion perception might abide the same physiological principles, but it is not known whether the neural substrates for the two processes overlap. We propose two hypotheses. First, VOR and perception have a common neural substrate. Second, there are nonoverlapping neural networks: one is involved in the perception and the other serves the VOR.

Methods: Experiment 1: We first measured the effects of 4-aminopyridine (4-AP) on motion perception and VOR in healthy subjects during constant velocity rotation steps. The scleral search coils were used to measure VOR, while subjects reported perceived angular velocity by spinning a hand-held joystick. 4-AP, a selective blocker of inward rectifier potassium conductance facilitates synchronization and precision of Purkinje neuron discharge and increases synaptic levels of GABA at brainstem and deep cerebellar vestibular neurons. Increased levels of GABA reduce the decay time constant of the perceived angular velocity and VOR. Experiment 2: In 14 subjects with cerebellar stroke, we asked whether specific location of the focal vestibulocerebellar lesion impairs the perception of motion but spares oculomotor function.

Results: Experiment 1: 4-AP reduced the decay time constant of perceived angular velocity and VOR. However, the amount of reduction was not the same. Unlike the VOR, the perceived angular velocity gradually built up and plateaued prior to decay. The results suggested the possibility of nonoverlapping or partially overlapping neural substrates for VOR and perception. Experiment 2: Six of 14 subjects with cerebellar stroke falsely perceived spinning of visual surrounds (vertigo), but their oculomotor function was normal. This group was called the "disease model." The remaining eight patients were symptomatic for vertigo, but they also had spontaneous nystagmus accounting for their symptom. The latter group was called the "disease control." Magnetic resonance imaging in both groups consistently revealed focal cerebellar infarct affecting lobule IX. In the disease model group, only the dorsal aspect of lobule IX was affected. However, the disease control group had complete involvement of lobule IX.

Conclusion: Motion perception and VOR abide similar physiological principles; however, the neural substrates for the two do not completely overlap. We speculate that perception-related vestibular neurons might be located in the dorsal aspect of cerebellar lobule IX. Strategic cerebellar strokes affecting dorsal lobule IX would therefore cause selective deficits in motion perception but normal oculomotor function and VOR.

Waveform Shape Suggests the Pathophysiology of Seesaw Nystagmus

Authors: Aasef G. Shaikh, MD; David S. Zee, MD; Mark F. Walker, MD

Background: We suggest that distinct features of eye movement trajectories classify seesaw nystagmus in four subtypes. Each subtype may have discrete pathophysiology and etiology. Seesaw nystagmus is a rare and distinct disorder of eye movement featuring conjugate torsional oscillations combined with dysjunctive vertical oscillations. The upward and intorting movement of one eye combined with the downward and extorting movement of the other eye resembles the action of a seesaw. Typically, the suprasellar or parasellar lesions cause seesaw nystagmus, but many other etiologies were also proposed.

Methods: We measured eye movements in eight patients who had seesaw nystagmus associated with various etiologies. Three dimensional search coils were used to measure eye movements. The eye position data was analyzed offline in custom-programmed software in Matlab.

Results: Shape and regularity of the waveforms classified the seesaw nystagmus in four types. Each type has distinct clinical feature, vestibular function and background neurological history. Type 1: One patient with this type of seesaw nystagmus had regular pendular oscillations, where upward moving eye intorted but simultaneously downward moving eye extorted. There was an increased gain of the torsional vestibuloocular reflex. The nystagmus was suppressed during eye closure or in a dark environment. The amplitude of pendular seesaw nystagmus was decreased with levetiracetam. These findings supported unstable visuo-vestibular interaction as an etiology of pendular seesaw nystagmus. Type 2: Three patients had conjugate torsional pendular nystagmus of comparable amplitude in both eyes, but the vertical pendular nystagmus had remarkable amplitude disparity. In such pendular seesaw nystagmus, the VOR gain was normal but the nystagmus amplitude attenuated in darkness. Gabapentin reduced the amplitude of pendular hemi-seesaw nystagmus in one treated patient. Type 3: Three patients had disconjugate and irregular oscillations along all three axes of rotation. The irregularity of vertical and torsional oscillations gave a "seesaw" appearance to their nystagmus. These three patients were diagnosed with oculopalatal tremor and had pseudohypertrophic inferior olive nucleus on magnetic resonance imaging. Type 4: One patient with Arnold Chiari malformation had jerk vertical and jerk torsional nystagmus. The torsional nystagmus was equal on both sides, but vertical nystagmus was dysjunctive. The vertical nystagmus in one eye modulated its amplitude and direction with orbital position of the globe. This nystagmus did not change after decompression surgery or treatment with baclofen. Impaired function of unilateral interstitial nucleus of Cajal, but normal rostral interstitial nucleus of medial longitudinal fasciculus explains jerk seesaw nystagmus.

Conclusion: Waveform characteristics classified seesaw nystagmus in four subtypes. Each subtype has discrete etiology and pathophysiology.

Anatomic Study of Fiber Tracts Linking the Basal Ganglia and Cerebellum in Patients with Parkinson Disease

Authors: Jennifer A. Sweet, MD; Benjamin Walter, MD; Jonathan P. Miller, MD

Objective: To radiographically evaluate white matter tracts connecting the basal ganglia to the cerebellum in patients with Parkinson disease (PD).

Background: Stimulation of white matter tracts in the vicinity of targeted structures may contribute to the observed therapeutic effects of deep brain stimulation (DBS) for PD. Two tracts linking the basal ganglia and cerebellum have been described in primates: the subthalamopontocerebellar tract (SPCT) and dentatorubrothalamic tract (DRTT). We used fiber tracking to evaluate white matter tracts that connect the cerebellum to the region of the basal ganglia in patients with PD who were candidates for DBS.

Methods: Fourteen patients with advanced PD underwent high-resolution magnetic resonance imaging, including diffusion tensor imaging, nine of whom subsequently underwent DBS of the subthalamic nucleus. For each side in each patient, two regions of interest were defined encompassing (1) the region of the basal ganglia, including the red nucleus and subthalamic nucleus; and (2) the contralateral cerebellum. Fiber tracking was performed using iPlan FiberTracking (BrainLab, Feldkirchen, Germany) software. The size of each tract was measured and, for patients who underwent implantation, the location of the tract relative to the cathodal electrode contact was determined.

Results: In each patient, two distinct white matter tracts were identified that corresponded to the described anatomic features of the SPCT and DRTT, respectively. In nine patients who presented with tremor, a significant relationship ($P < 0.001$) was found between the side with the larger DRTT and the side of greater tremor amplitude. In thirteen of the sixteen implanted electrodes (81%), the active contact was traversed by the DRTT and its average distance from the DRTT in the remaining three electrodes was 2.61 +/- 0.81 mm.

Conclusion: The SPCT and DRTT may be related to the expression of the symptoms of PD, which have implications for DBS targeting.

The Use of Aripiprazole to Alleviate Obsessive Compulsive Symptoms in Patients with Schizophrenia on Clozapine Treatment

Authors: Erum Ahmad, MD; Blessing Igboeli, MD; Irina Korobkova, MD

Background: We review the literature on concurrence of Obsessive Compulsive Disorder (OCD) with schizophrenia and review the theoretical mechanism by which clozapine can cause worsening of OCD. We also discuss the potential mechanism by which aripiprazole can result in improvement of OCD symptoms in such a patient population. Various studies have reported that up to 30% of patients suffering from schizophrenia also suffer from symptoms of OCD. However, research data show that treating some schizophrenic patients with antipsychotics, specifically clozapine, may result in worsening of their OCD symptoms. Such studies have shown that there is some benefit with aripiprazole in improving OCD symptoms.

Methods: We conducted a review of relevant research data and journal articles found on PubMed and Ovid.

Results: The patient's symptoms were alleviated by adding aripiprazole to the current treatment regimen.

Conclusion: Providers should be aware of the potentiation of OCD symptoms with the use of antipsychotics, specifically clozapine. Adding aripiprazole to the treatment regimen of such patients should be considered.

Severe Dysarthria: A Harbinger of Myositis

Authors: Kelly Andrzejewski, DO, PhD; Mark L. Cohen, MD; Bashar Katirji, MD

Background: We report a patient with inflammatory myopathy presenting with severe dysarthria accompanied by dyspnea and dysphagia. Inflammatory myopathies often present with limb weakness, myalgia and elevated creatine kinase (CK). Dysphagia is the most common bulbar symptom, occurring in up to a third of patients.

Case Description: A 72-year-old woman, with a history of hypertension and hyperlipidemia, was initially admitted with progressive dyspnea and to rule out pulmonary embolism. She was readmitted one month later with severe dysphagia and dysarthria and persistent dyspnea. She reported a 10-pound weight loss over two months prior to admission in the setting of minimal oral intake due to decreased appetite and eventual development of dysphagia. Her neurologic examination revealed severe flaccid dysarthria and mild proximal left upper extremity weakness, which was attributed to left shoulder arthroplasty. Otherwise, the cranial nerve and motor examination was normal. Specifically, her tongue appeared normal with no atrophy or enlargement. CK was elevated at 1112 U/L (normal 0 – 215 U/L). The following studies were unremarkable: computed tomography scan of the neck and chest, laryngoscopic exam, magnetic resonance imaging of the brain, cerebrospinal fluid cell counts, chemistries, cytology, paraneoplastic antibodies panel, acetylcholine receptor antibodies, and slow repetitive stimulations of the median and spinal accessory nerves. Needle electromyography showed myopathic motor unit action potentials and fibrillation potentials in shoulder girdle muscles, particularly the deltoid. A right deltoid muscle biopsy demonstrated a microvasculitis with muscle fiber degeneration and satellite cell activation. There were occasional acutely denervated fibers and no inclusion bodies. Based on these findings, diagnosis was consistent with an idiopathic inflammatory myositis. The patient required percutaneous endoscopic gastrostomy (PEG) placement for nutrition. Treatment with intravenous methylprednisolone followed by daily oral prednisone significantly improved her dysarthria, and CK normalized by one month after initiation. By three months, there was minimal dysarthria and dysphagia and her PEG tube was removed.

Conclusion: Dysarthria should be added to the myriad of presenting features of inflammatory myopathies. Dysarthria has only rarely been reported in myositis, especially as one of the main presenting symptoms. In a review of the literature, case reports that mentioned dysarthria as a symptom associated with myositis often involved atrophy or enlargement of the tongue, which was not observed in this patient.

Antiepileptic Drug Refill Compliance, Medicaid Insurance Gaps and Emergency Room Visit

Authors: Paul M. Bakaki, MD; Siran M. Koroukian, PhD; Catherine M. Stein, PhD; Kitti Kaiboriboon, MD; Jeffrey M. Albert, PhD

Background: We assess the causal effect of antiepileptic drug (AED) refill compliance on emergency department (ED) visits among epilepsy patients in the presence of insurance gaps, and investigate whether this effect varies with race, age, comorbidity, disability or concomitant medications. Adequately used AEDs control seizures and mitigate complications in the majority of persons with epilepsy, but 30% to 50% of the patients are noncompliant with prescription instructions. Noncompliance with AED potentially increases health care utilization, such as visits to the ED. The effect of AED noncompliance on ED visit may differ if individuals with insurance gaps are included in the study population.

Methods: We conducted a retrospective cohort study of adults with epilepsy using the Ohio Medicaid enrollment and claims data of 2002 through 2005. From the pharmacy claims, we estimated the medication possession ratio (MPR) of any of 15 different AEDs as the sum of days of AED supplied in a refill interval/number of days in the refill interval. The conventional MPR cut-off of less than 0.8 was considered noncompliant refill. Revenue center codes, place of service and CPT codes were used to ascertain ED visit from outpatient, inpatient or physician claims. Using history-adjusted marginal structural models, we estimated the causal effect of three-month cumulative AED refill compliance on ED visit in the presence of insurance gaps.

Results: 40,276 epilepsy patients contributed 1,130,584 months of observation, with a median of 31 months, interquartile range of 13 – 44, and mean of 28.1 (15.4). 24.0% (271,376) of observed months had an MPR less than 0.8. ED visit for any reason occurred during 12.2% (137,409) while epilepsy-related ED visit occurred during 1.4% (16,236) of the months. Every AED nonfilled month increased the risk of ED visit for any reason by 19% (Adjusted Incidence Ratio (AIR) 1.19, 95% CI 1.18 – 1.20). This effect was the same whether all available data, only the first insurance block, or only individuals continuously insured were included in the analysis, albeit at a small loss of statistical power. However, it increased to 23% among individuals younger than 55 who had comorbidity and decreased to 12% among older individuals with comorbidity. The risk for epilepsy-related ED visit was increased by 15% (AIR 1.15; 95% CI 1.13, 1.18) for every non-AED filled month.

Conclusion: Health care providers and caregivers of people with epilepsy who are on Medicaid programs, especially younger adults with comorbidity, should ensure compliance with AEDs to mitigate ED visits. When using administrative data to apply causal inference methods, it is advisable to use all available data or censor study subjects at the first insurance gap rather than use only the continuously insured.

Jeavons Syndrome – Seizing the Light

Authors: Abdelrahman Beltagy, MD; Asim Shahid, MD; Ingrid Tuxhorn, MD

Background: We performed electroclinical analysis of the clinical spectrum and the visual/photic stimuli relevant for treatment of eyelid myoclonia (EM) with and without absences (Jeavons syndrome). EM with and without absences, eye closure-induced seizures with electroencephalogram (EEG) paroxysms, and photosensitivity are the electroclinical triad characterizing Jeavons syndrome described in 1977. Onset is typically in childhood with a peak at 6 – 8 years. Delayed diagnosis is not uncommon because EM is often misinterpreted as tics or mannerisms.

Methods: Four patients with the electroclinical features of Jeavons syndrome were found in our EEG database from 2010 to 2012.

Results: Seizure onset was age 5 – 14 years. Diagnosis was delayed in all. Facial tics, syncope and OCD were the most frequent misdiagnoses. Comorbidities included learning disability and attention deficit hyperactivity disorder in three of four patients. Frequent eyelid myoclonias with absences were seen in all, and generalized tonic-clonic (GTC) seizures were seen in three of four patients. One patient sustained a severe hot water scald during a GTC seizure prior to correct diagnosis and treatment with valproic acid (VPA). Obsessive reflex self-induction of seizures was seen in all (e.g., waving hand in front of one eye with secondary eyebrow alopecia, seeking out lights, looking into the glare of snow or sunshine on water). EEG showed spontaneously generalized spikes activated by eye closure and photoparoxysmal response. GTCs responded well to VPA, while EM was medically refractory in all. Light intensity reduction with tinted contact lenses and sunglasses resulted in a greater than 90% reduction in EM. In two patients, obsessive self-induction responded to cognitive behavioral therapy.

Conclusion: Delayed diagnosis in Jeavons syndrome may not be uncommon due to the brief and subtle nature of the EM. Misdiagnoses such as tics, OCD or syncope may carry a significant safety risk and put patients at risk for mild cognitive comorbidities due to untreated epileptogenesis. Multimodal treatment with AEDs, light intensity reduction and CBT appears promising.

HIV Vasculitis: A Case of an HIV Patient with Both Hemorrhagic and Ischemic Infarct

Authors: Oladi Bentho, MD, MS; Michael DeGeorgia, MD; R. John Leigh, MD

Background: Our objective was to determine the mechanism of stroke in patient with human immunodeficiency virus (HIV). HIV infection is known to cause various neurological complications, including stroke. The incidence of stroke is reported to be between 1% and 5% in clinical series, although a higher proportion (4 – 34%) has been reported in postmortem studies. Ischemic infarct is more frequent than hemorrhagic infarct. According to Ovbiagele and Nath, ischemic stroke was the predominant pathological stroke type and the proportion of patients with ischemic stroke among HIV patients doubled between 1997 and 2006. In a South African hospital based study of stroke patients, 96% of the HIV positive group (67) had ischemic stroke and 4% had hemorrhagic infarct. Out of the 64 patients in the ischemic group, the subtypes were lacunar stroke (n = 13), partial anterior circulation stroke (n = 33), total anterior circulation (n = 11), and posterior circulation stroke (n = 11). HIV increases the risk of both ischemic and hemorrhagic infarct via several mechanisms, including cardioembolism, coagulopathy, opportunistic infections, vasculitis and primary HIV vasculopathy.

Case Description: We present a case of a 56-year-old right-handed Caucasian female with HIV that presented with a one-week history of headache, new onset left hemiparesis, left facial droop and generalized tonic clonic seizure. Systolic blood pressure on admission was 200 mmHg. She had a computed tomography (CT) scan of the head that showed a right frontal lobe hemorrhage, which is not a classical location for hypertensive hemorrhage. To determine the mechanism of her infarct, she had a series of studies that included transthoracic echocardiogram, magnetic resonance imaging (MRI) of the brain, magnetic resonance angiography of the head and neck, and cerebral angiogram. Her cerebral angiogram showed focal dilatation and narrowing in the distal right frontal polar branches with downward displacement of distal vessels of the anterior cerebral artery in the region of known hemorrhage. This finding was consistent with vasculitis or vasculopathy. She underwent an extensive work-up including a lumbar puncture that was negative for an opportunistic infection; a work-up for vasculitis was also negative. She had a follow-up CT scan of the head that revealed a new left frontal hypodensity, which was diffusion restriction positive on an MRI of the brain. She had a right frontal open biopsy, which did not show evidence of vasculitis.

Conclusion: We report a case of an HIV patient with both hemorrhagic and ischemic infarct, with cerebral angiographic findings consistent with a central nervous system vasculitis, but a work-up for vasculitis, including a biopsy, was negative. Studies have found that 60% of biopsies in patients suspected of CNS vasculitis with a positive angiogram are negative. We concluded that our patient likely has HIV vasculitis. She was treated with steroids and responded well.

Five-Year Evaluation of Consultation-Liaison Psychiatry Referrals in a Tertiary Medical Center

Authors: Pu Cheng, MD; Jeanne Lackamp, MD

Background: Our objective was to determine the consultation-liaison psychiatry referral pattern and changes at University Hospitals Case Medical Center and compare them with other general hospital patterns reported in literature by studying the referral cases (total 7,063) in the past five years (2007 – 2011). The study is approved by the University Hospitals Institutional Review Board. In the era of global mental health challenges, psychiatric disorders take a heavy toll both independently and in combination with medical conditions. Psychosomatic medicine (consultation-liaison psychiatry) is well-positioned on the front line of medicine by contributing expertise in integrating and exploring the interface of psychiatry and medicine. However, few studies evaluate the evolution of this subspecialty in a large scale over time.

Methods: Psychiatric consultations within a metropolitan tertiary hospital in the United States over five consecutive years were collected and analyzed. Multiple psychiatric variables were reviewed, including patient demographic data, reason for referral, psychiatric diagnosis and recommended management. At this time, only 2007 preliminary data is available for presentation; analysis of the other years is ongoing.

Results: The study includes 7,063 psychiatric consultation cases from 2007 to 2011 (1,134 cases from 2007; 43.2% males and 56.8% females, with 28% older than 65). Through the five years, annual consultation rates increased from 3.4% to 6.4% of total adult inpatient medical/surgical hospitalizations, which is much higher than the 0.9 – 1.7% reported in other literature. Depression remains the most common reason for referral, which is consistent with other published studies. Substance use issues and confusion are the next two most common consultation questions in our study, while anxiety followed depression in other studies. Among our consultation recommendations, nonpharmacologic approaches (psychotherapy, music/chaplain service, support, social arrangement such as determining capacity or filling documents for guardianship) are most common, while antipsychotic and antidepressant medication recommendations share the second position.

Conclusion: Although the project is still in progress, data from 2007 show slightly more consultations for female than male patients as well as a fairly large percentage of elderly (older than 65) patients; depression is our top consultation reason, which is consistent with other studies. Interestingly, our consultation rate is much higher than reported in other studies, and it has been consistently rising in the five years analyzed. Consultation patterns and shifts will be revealed once the entire study is finished. Determining patterns of psychiatric consultations will inform future directions for service provision and educational opportunities.

Neurosarcoidosis Presenting as Trigeminal Neuralgia Due to an Intracranial Extra-Axial Neurosarcoid Mass: Case Report and Review of the Literature

Authors: Rachel Colman, MD; Michael Devereaux, MD; Nicholas C. Bambakidis, MD

Background: We present a case of neurosarcoidosis presenting with trigeminal neuralgia due to an intracranial extra-axial neurosarcoid mass, and we review the literature revealing that intracranial extra-axial neurosarcoid mass lesions are rare and an infrequent cause of a cranial nerve mononeuropathy. Sarcoidosis is an inflammatory granulomatous disease that affects multiple organ systems. Neurosarcoidosis can be seen in approximately 5 – 15% of patients with systemic sarcoidosis, though it is often underdiagnosed. Intracranial extra-axial masses are very rare and often misdiagnosed.

Methods: We reviewed the relevant literature and presented a case of neurosarcoidosis presenting as trigeminal neuralgia, which related to an intracranial extra-axial mass and responded to medical therapy.

Results: Neurosarcoidosis needs to be considered when approaching these types of lesions as they can mimic other intracranial lesions, especially given that medical therapy can be effective and surgical resection is not always necessary.

Conclusion: Empiric corticosteroid therapy can be used for intracranial mass lesions and was seen to be effective in reducing the size of the lesion in our patient.

Bielschowsky and the Neurology of Eye Movements of the Blind

Authors: Sylvia Eisele, MD; Rosalyn Schneider, MD; R. John Leigh, MD

Background: We investigated the neural origin of the Heimann-Bielschowsky phenomenon. Alfred Bielschowsky was a pioneer in ocular motor research. Greatly respected as chairman of ophthalmology in Breslau, Germany, he lost his position in 1933 after the National Socialist Party came to power. He immigrated to the United States where he joined the Dartmouth Eye Institute. From this base, he transformed concepts of eye movements in the United States through a series of influential lectures and articles that laid down the basic physiological principles that had been established by Hering and Helmholtz. We focused on one of his contributions: monocular gaze instability in an eye with loss of vision, manifested by slow pendular eye movements in the vertical plane, known as the Heimann-Bielschowsky phenomenon.

Methods: To investigate the neural mechanism of the Heimann-Bielschowsky phenomenon, we measured eye movements in an individual who, as a child, had lost the lens of one eye due to trauma. We used the magnetic field/search coil technique and compared gaze stability with a group of normal subjects and with a patient who had been blind in both eyes since birth due to Leber's congenital amaurosis. We also reviewed the German and English literature.

Results: Heimann and von Graefe propose that gaze stability in an eye with impaired vision would improve if that eye were forced to view (by having the other eye covered). We confirmed this prediction and also found, unexpectedly, that gaze stability in the good eye decreased, with predominantly vertical oscillations. Normal subjects showed similar gaze stability, whichever eye viewed. A patient with bilateral blindness showed bilateral gaze instability with continuous drifts of her eyes.

Conclusion: Our results can be best explained in terms of the neural network (neural integrator) in the brainstem and cerebellum; component neurons encode the position of individual eyes. Binocular visual input is crucial to continuously tune this neural network. Whereas monocular visual loss causes gaze instability predominantly in the affected eye, binocular loss of vision causes bilateral gaze instability. However, restoration of vision (e.g., by gene therapy for Leber's congenital amaurosis) has the potential to improve both vision and gaze stability.

Cerebral Capillary Malformation-Arteriovenous Malformation – a Rare Genetic Disorder Due to RASA1 Mutation with Stroke-Like Presentation

Authors: Deepak Gulati, MD; Asim Shahid, MD; Sunil Manjila, MD; Nicholas C. Bambakidis, MD

Background: We demonstrate a link between RASA1 mutation and cranial vascular malformation and demonstrate vascular steal phenomenon to support a vascular seizure and epilepsy model in the presence of high-flow vascular lesions. Capillary malformation (CM) – arterial venous malformation (AVM) is a rare, newly recognized syndrome caused by heterozygous mutations in RASA1 gene. RASA1 gene encodes protein activator 1, which is essential for endothelial cells to form into highly organized networks. Mutations of the RASA1 gene (Ch 5q13.3.1), which signals angiogenesis, have recently been described in patients with various CM-AVM phenotypes. Cutaneous CMs and combined vascular anomalies are seen in Sturge Weber, Klippel-Trenaunay and Parkes-Weber syndromes. Small, usually multifocal and randomly distributed atypical cutaneous CMs previously reported as classic cutaneous manifestations of RASA1 mutations occur in association with fast flow anomalies, namely AVM and arteriovenous fistula (AVF), in approximately 18.5% of affected families. We describe successful surgical treatment of a 3-year-old, with cutaneous and intracerebral lesions consistent with CM-AVM due to RASA1 mutation, who presented with stroke-like seizure events.

Methods: A 32-month-old boy presented with macrocephaly. Five months later, he started developing multiple episodes of falls, loss of awareness, and loss of strength in the right arm and leg, with right arm clonic activity. He was unable to move the right side of his body with intact awareness. He was noticeably left-handed by about 6 months of age. Large left facial CMs, with additional lesions on the left side of the neck, were noted on exam. His head circumference was above the 95th percentile. An examination revealed a right hemiparesis. Video electroencephalogram showed frequent spikes and seizures arising from the left hemisphere. Magnetic resonance imaging of the brain showed a hypoplastic and malformed left parietal lobe with polymicrogyria and gliosis, with a highly abnormal vasculature due to an AVM. A conventional angiogram confirmed the presence of an extensive left parietal pial AVF. A left craniotomy with resection of the lesion was performed; no filling of the AVF was seen on postoperative angiogram. Biopsy of the facial lesion showed CMs, and genetic testing was positive for RASA1 gene mutation.

Results: Though the focal clonic seizures were thought to be due to an underlying hypoplastic/gliotic left parietal lobe with polymicrogyria, the episodic stroke-like hemiparesis persisted outside the window of Todd's palsy and with a small dosage of levetiracetam. The episodic hemiparesis was thought to be due to steal phenomenon caused by high-flow pial AVF, leading to a decrease in arterial supply with an underlying cortical pathology.

Conclusion: CM-AVM may be seen in a number of well-described syndromes. However, a link between RASA1 mutation and cranial vascular malformation has been demonstrated, as has a vascular steal phenomenon in a pediatric patient with CM-AVM, where hemiparesis was more pronounced in the setting of seizure, possibly due to the need for increased cortical perfusion. The presentation is common in high-flow vascular lesions. It supports the vascular seizure and epilepsy model reported in Sturge Weber and may have implications for innovative therapies.

Root Cause Analyses of Preventable Causes of Readmission after Stroke: the University Hospitals Case Medical Center and UH System Stroke Program Experience

Authors: Benny S. Kim, MD; Julie Fussner, MD; Cathy Sila, MD

Background: We evaluate the root cause analyses 30-day readmission rate after stroke. Metrics, such as the 30-day readmission rate after stroke, are increasingly used by consumers and payors to reflect hospital quality of care. Benchmarks determined by large administrative databases lack detailed root cause analyses, which are crucial in determining preventable causes.

Methods: In 2010, the UH System Stroke Program (UHSSP) Quality Initiative developed a MIDAS™ report alerting the Stroke Coordinator of all inpatient encounters to any UH hospital within 30 days of a stroke discharge from University Hospitals Case Medical Center. A focus study guided a detailed case review, including demographics, index admission stroke subtype, discharge treatment and disposition, follow-up appointments, medical compliance, readmission diagnosis and location, and Root Cause Analysis of preventable causes of 1,093 stroke discharges from January 2011 to June 2012. During this period, compliance with evidence-based guidelines for stroke exceeded benchmarks.

Results: Of 1,093 stroke discharges from January 2011 to June 2012, 30% were older than 80 years and 45% were readmitted from extended care facilities. The 30-day all-cause readmission rate was 5.7% to UH Case Medical Center and 2% to a UH system community hospital; this rate included a 30-day readmission rate for recurrent stroke or TIA of 1.1%. Stroke subtypes of readmitted patients reflected our stroke population: 78% ischemic stroke, 9.6% transient ischemic attack, 8% intracerebral hemorrhage, and 3.6% subarachnoid hemorrhage.

Conclusion: The 30-day stroke and all-cause readmission rates were well below published rates. However, without our UH systems report, we would have missed 26% of the readmissions that went to community hospitals in our regional network. The Root Cause Analyses of readmitted patients discovered evidence relevant to the readmitting diagnosis prior to index hospital discharge in 7% but, in retrospect, only 6% of readmissions were felt to have been preventable by the discharging team. Recurrent vascular events were the most common cause of readmission despite the fact that compliance with evidence-based care exceeded benchmarks during this period. It is possible that effective patient education enhanced the recognition of vascular signs and symptoms that warranted readmission. Measures directed at preventing vascular events and infections 30 days after discharge may have an important medical and fiscal impact for hospitals and the patients they serve.

Computed Tomography or Magnetic Resonance Perfusion Imaging Benefits Selection of Acute Ischemic Stroke Patients for Endovascular Treatment

Authors: Arshneel S. Kochar, BA; Richard S. Jung, MD; Brian Koo, MD; Sunil Manjila, MD; Benny S. Kim, MD; Kristine A. Blackham, MD; Jeffrey L. Sunshine, MD

Background: We compare the clinical outcomes between patients who did and did not receive advanced multimodal imaging prior to endovascular treatment of acute ischemic stroke. The predictability of perfusion imaging in selecting patients for endovascular treatment of acute ischemic stroke (AIS) remains controversial. Computed tomography (CT) and magnetic resonance (MR) perfusion have been performed at our institution during AIS evaluation to predict which patients would likely benefit from endovascular therapy.

Methods: From April 2004 to July 2012, 330 patients with large vessel AIS were retrospectively reviewed and divided into three cohorts: (1) perfusion with mechanical thrombectomy (MT) and/or intra-arterial thrombolysis (IAT) (n = 98); (2) no perfusion with MT and/or IAT (n = 191); and (3) perfusion and no endovascular treatment (n = 41). Cohorts were compared based on neurologic improvement (greater than or equal to a four-point change in National Institutes of Health Stroke Scale score [NIHSS]), successful revascularization (Thrombolysis in Myocardial Infarction score of 2 – 3), symptomatic intracranial hemorrhage (sICH), modified Rankin Scale (mRS) less than or equal to 3 on discharge, and in-hospital mortality. Multivariate regression was performed to determine the predictive value of perfusion imaging prior to endovascular therapy.

Results: Of 289 treated patients, mean age was 67 and median initial NIHSS was 17. The treated groups were matched in baseline characteristics; they had similar revascularization rates and favorable outcome by mRS or change in NIHSS. No mortality difference between the untreated and treated cohorts was seen but, of the treated patients, 10 of 98 with perfusion imaging expired compared to 48 of 191 without perfusion (P = 0.01). Logistic regression showed patients who had perfusion prior to endovascular therapy were less likely to die during hospitalization (OR = 0.267) or to develop sICH (OR = 0.269). Other predictors of mortality included advanced age (OR = 1.086) and high initial NIHSS score (OR = 1.142).

Conclusion: Patients who underwent CT or MR perfusion imaging prior to neurointervention for AIS were less likely to suffer sICH or in-hospital mortality. These imaging modalities are preferable methods for selecting patients likely to benefit from endovascular treatment.

Medtronic Driver Balloon-Mounted Coronary Stent System in Endovascular Neurointervention: Off-Label Clinical Experience at a Tertiary Referral Center

Authors: Sunil Manjila, MD; Richard S. Jung, MD; Benny S. Kim, MD; Daniel P. Hsu, MD; Kristine A. Blackham, MD; Robert Tarr, MD; Jeffery L. Sunshine, MD

Background: We review clinical experience with the Medtronic Driver® balloon-mounted coronary stent for use in neurointervention. Balloon-mounted coronary stents have been employed in the endovascular management of ischemic cerebrovascular disease, where rapid and precise stenting with angioplasty may be performed in a patient with minimal or no sedation. The Medtronic Driver® balloon-mounted stent is known to have excellent trackability and deliverability, making it a viable tool in the armamentarium of the neurointerventional surgeon.

Methods: We conducted a retrospective review of 46 patients who underwent endovascular revascularization utilizing Medtronic Driver® stent from 2003 to 2011. The characteristics analyzed were patient demographics, lesion location, etiology of vascular lesion, degree of stenosis, extent of revascularization, short-term complications and clinical outcome.

Results: Out of 46 patients with 51 Driver® stents studied, 21 were female and the age of patients ranged from 37 to 91 years. The treatment data was composed of 22 internal carotid artery stents (19 patients), one common carotid artery stent, 25 vertebral artery stents (20 patients), and three basilar arteries. 18 of 51 stents were intracranial, including seven internal carotid artery stents, three basilar artery stents, and eight vertebral artery stents. Of the extracranial stents, there was one common carotid artery stent, 15 internal carotid artery stents, and 17 vertebral artery stents. The etiology of the lesions included 41 strokes or transient ischemic attacks, with symptomatic stenosis, one in-stent restenosis, and four dissections. Five patients had occluded vessels, five had a less than 70% stenosis, and 36 patients had 70 – 99% stenosis. The Driver® stent dimensions ranged from 3 mm x 9 mm to 4 mm x 24 mm. Driver® stent failed in two cases, and four patients developed in-stent restenosis; two of them were stent occlusions in the same patient. Multiple Driver® stents were used in five patients. Three patients developed symptomatic post-stenting hemorrhages, and four patients died from medical complications unrelated to the procedure.

Conclusion: This study presents the largest single institutional review of the Medtronic Driver® balloon-mounted coronary stent for use in neurointervention. The authors have demonstrated technical feasibility of the stent system and satisfactory revascularization in a variety of clinical indications. This device allows quick revascularization by performing stent and angioplasty together and providing access for distal clot removal.

Analog Restless Legs Syndrome Rating Scale – A Novel Bedside and Clinic Tool

Authors: Prachi Mehndiratta, MD; Aasef Shaikh, MD; Carmela Gonzales, MD; Brian Koo, MD

Background: We evaluate the co-administration of Analog Restless Legs Syndrome rating scale (ARLS) with the International Restless Legs Severity Scale (IRLS) to determine how well components of the ARLS correlate with the IRLS score. Restless legs syndrome (RLS) is a common movement disorder characterized by an inescapable urge to move the limbs during evening hours. Visual analog scales are used to determine severity of discomfort in RLS; however, analog measures have not been compared to overall severity based upon the more widely used IRLS.

Methods: Monthly ARLS and IRLS questionnaires were administered to untreated subjects with RLS who were enrolled as part of a prospective study approved by an institutional review board. The ARLS comprised the general severity of symptoms, the urge to move, and alleviation of symptoms by movement (each scored from 0 to 100). The relationship between the normalized total IRLS score and the normalized total and subscores of the ARLS was assessed.

Results: Twenty-six subjects with idiopathic, untreated RLS were studied. Mean age was 49.1 +/- 5.6 years, and 84.7% were Caucasian. The average total IRLS score was 14.1 ± 5.8, while the mean value of ARLS, averaged over its three components, was 43 ± 22.5. The relationship between normalized overall severity component of the ARLS and normalized IRLS was optimally described with a linear function; the correlation coefficient was 0.6 and slope was 1.2. The relationship between the urge to move and IRLS score was best described by a sigmoid function. A negative correlation between RLS severity measured with IRLS and improvement following movement was observed and residual symptoms after movement positively correlated with the normalized IRLS score.

Conclusion: We conclude that the ARLS has comparable efficacy to IRLS in estimating overall disease severity. It is rapidly administered and easily interpreted by the subjects. Further studies are necessary to determine its use in temporal assessment of patients on treatment for RLS.

Ischemic Stroke in Patients with Atrial Fibrillation Failing Warfarin Therapy

Authors: Prachi Mehndiratta, MD; Murad Talahma, MD; Yonatan Spolter, MD; Cathy Sila, MD

Background: We evaluate the mechanisms and management of ischemic stroke despite therapeutic warfarin anticoagulation in patients with atrial fibrillation (AF). Patients with AF are educated on the risks of thromboembolic events and excess bleeding with inconsistent warfarin use, but little is known about "warfarin failure" in patients with AF who are compliant with their regimen.

Methods: Patients with ischemic stroke admitted to University Hospitals Case Medical Center between July 2009 and July 2011 were retrospectively reviewed for warfarin use, compliance, level of anticoagulation, demographics, risk factors, interventions and medications on discharge. The review was conducted under approval from the Institutional Review Board. Stroke mechanism was classified using the calculator for the trial of ORG 10172 in acute stroke treatment (TOAST).

Results: Consistent warfarin use was reported in only 21.2% (44/208) of patients presenting with ischemic stroke and AF; 31.8% of these cases were therapeutic and 61.8% subtherapeutic on treatment. Therapeutic patients were significantly more likely to have valvular heart disease (28.5% vs. 0%, P = 0.003) and hypertension (OR 3.4615 CI 0.37 – 31.56) and were younger, with higher CHADS2 scores (2.85 vs. 2.63), more severe stroke (13.06 vs. 10.26 on the National Institutes of Health Stroke Scale) and discharge to a facility (86% vs. 57%, P = 0.06). There was no difference in the rates of prior stroke, diabetes or coronary disease. Stroke mechanism by TOAST criteria was cardioembolic in only half of patients (evident 14.2%, possible 35.7%), with the remainder composed of lacunar (14.2%), large artery atherosclerosis (7.1%), and cryptogenic (28.5%) mechanisms. Management strategies included discharge on adjusted dose warfarin (62%), alternative oral anticoagulant (8%), carotid stent (8%), and discontinuation of warfarin (23%) due to bleeding complications during the hospitalization.

Conclusion: There are no recommendations in the guidelines for patients with AF and stroke failing warfarin therapy. For patients with valvular disease, the intensity of anticoagulation can be increased; however, alternative causes may account for a significant proportion of strokes in these patients, and recommendations for therapy should be individualized based upon a thorough evaluation.

Clues to the Mechanism of Wake-Up Stroke

Authors: Prachi Mehndiratta, MD; Aki Tanimoto, MD; Eileen Zhuang, MD; Brian Koo, MD

Background: Our objective was to determine if characteristics of wake-up stroke (WUS) differed from strokes occurring during wakefulness and if persons suffering from WUS were more likely to have obstructive sleep apnea. The relationship between ischemic stroke and obstructive sleep apnea (OSA) is complex. OSA is an independent risk factor for incident stroke and is associated with poor neurologic recovery following stroke. Stroke occurring during sleep, or WUS, is common, accounting for about one-quarter of all ischemic strokes.

Methods: Fifty-three subjects with ischemic and hemorrhagic stroke were studied. Subjects completed questionnaires screening for OSA (Berlin questionnaire) and assessing sleep characteristics. Other collected data included age, gender, stroke severity (National Institutes of Health Stroke Scale [NIHSS]), stroke localization and mechanism.

Results: WUS occurred in 22 out of 53 subjects (41.5%): one of eight (12.5%) hemorrhagic strokes and 21 of 45 (43.8%) ischemic strokes. Positive screening for OSA by Berlin questionnaire occurred in 33 out of 53 subjects (62.3%): 66.7% of WUS and 47.8% of non-WUS among the ischemic stroke subjects (P = 0.21). Of those suffering ischemic stroke, subjects with WUS were significantly younger (62.0 ± 16.8 vs. 71.2 ± 13.0; P = 0.048) and trended toward having higher low-density lipoprotein levels (124.6 ± 41.5 vs. 106.0 ±3 9.0; P = 0.07). WUS patients were significantly less severe by NIHSS (3.7 ± 4.7 vs. 8.2 ± 7.5; P = 0.02) and those suffering WUS reported fewer hours of total sleep time at night (6.2 ± 3.5 vs. 8.0 ± 2.3; P = 0.06). Small vessel ischemic strokes occurred more commonly in WUS, though the difference was not statistically significant (47.4% in WUS and 29.2% in non-WUS; P = 0.21).

Conclusion: WUS is common among ischemic strokes and is associated with less severe neurologic deficit. Persons suffering WUS report fewer hours of habitual sleeping time but are not more likely to screen positive for sleep apnea. Additional research is needed to determine whether mechanistic differences exist between WUS and non-WUS and if WUS relates to sleep apnea.

Treatment of Multiple System Atrophy with Electroconvulsive Therapy

Authors: Benjamin Miller, MD; Asima Husain, MD; Sarah Ialacci, MD; Benjamin Walter, MD; Keming Gao, MD; Gisela Chelimsky, MD; Thomas Chelimsky, MD

Background: We evaluate the efficacy of electroconvulsive therapy (ECT) in the treatment of multiple systems atrophy (MSA) in a small pilot trial. MSA is a progressive neurodegenerative disorder encompassing autonomic, extrapyramidal, cerebellar, and pyramidal features. Extrapyramidal involvement (termed MSA-P, for Parkinsonian) is about three times more common than cerebellar involvement (termed MSA-C for cerebellar). Occasional patients feature both types. MSA strikes both genders equally at a mean age of onset of 53 years, the peak of productive life. Prognosis in MSA is poor. The most common causes of death in patients with MSA are pulmonary embolus, apnea and intercurrent infection. The pathophysiology of MSA is unknown and no cure exists, so management continues to be symptomatic. This study seeks to expand on an independent report of an MSA patient who had dramatic improvement in bladder function as well as mobility following treatment for his concomitant major depressive disorder with ECT. Glial-derived neurotrophic factor (GDNF) has been shown to elevate in ECT treated individuals. In MSA, GDNF was the main growth factor depleted in the frontal lobes of MSA patients, and repletion studies in animals improves their clinical picture. Therefore, it would seem prudent to attempt to increase GDNF via ECT in MSA patients and monitor for clinical improvement.

Methods: Three patients with MSA at mid-disease, with limited ambulation and age 40 – 80 years, were enrolled in a six-week trial of twice weekly ECT. Exclusions included dementia, pregnancy, coexisting serious neurologic disorder, and unstable or newly diagnosed medical or psychiatric disorder. Functional outcome measures included motor function with United Multiple System Atrophy Rating Scale (UMSARS), combined history and examination tool, brief Composite Autonomic Symptom Scale (COMPASS), autonomic testing, and cerebrospinal fluid (CSF) and serum levels of GDNF and brain-derived neurotrophic factor (BDNF).

Results: Of the three patients, UMSARS historical review scores showed overall improvement for all three. UMSARS Part II motor function showed improvement for two patients and mild worsening in one. UMSARS part III autonomic symptoms were improved in two patients. UMSARS part IV global disability score showed mild improvement in two patients. Autonomic testing did not show clear improvement, and COMPASS was equivocal. Serum and CSF BDNF and GDNF levels did not show a consistent trend.

Conclusion: ECT produced functional improvement that did not correlate with increases in GDNF or BDNF as had been hypothesized. The study was limited by a small sample size and short follow-up that may change with a larger series and longer duration of ECT. A larger, multicenter trial would be required to determine the role of ECT in MSA.

Increase in Rate of Pediatric Epilepsy Surgery Following Evidence-Based Guidelines

Authors: Elia Pestana-Knight, MD; Nicholas Schlitz, MD; Paul M. Bakakiv, Siran M. Koroukian, MD; Kitti Kaiboriboon, MD

Background: We measured changes in the rate of pediatric epilepsy surgery in the United States, coinciding with the publication of evidence-based guidelines. Epilepsy surgery is safe and effective and can lead to significant improvements in quality of life for persons with medically uncontrolled epilepsy, but utilization remains low. Evidence-based guidelines published in 2003 called for referral of these patients for evaluation as possible surgical candidates, but studies have shown no significant increase in utilization of surgery among adults. Temporal trends in the rate of pediatric epilepsy surgery have not been investigated at the population level.

Methods: We conducted a retrospective cross-sectional study using the Kids Inpatient Database from 1997, 2000, 2003, 2006 and 2009. Annual estimates of the number of pediatric epilepsy surgical procedures in the United States among children age 0 to 18 were derived using sample weights. Subgroup variables of interest include age group, gender, race/ethnicity, primary payer, hospital characteristics and surgery type. Annual rates of epilepsy surgery per 1,000 person-years were calculated using published prevalence estimates of pediatric epilepsy as the denominator. Linear regression was used to test for changes in rates over time.

Results: The rate of epilepsy surgery increased steadily from 1997 (0.83 surgeries/1000 person-years) to 2000 (0.87/1000), 2003 (1.24/1000), 2006 (1.43/1000) and 2009 (1.48/1000). The rate of surgery increased from 1997 to 2009 across all age groups, race categories, gender and payer types. Rates were lowest among African-American patients compared with white patients (0.62/1,000 vs. 1.20/1,000 in 2009), Medicaid-enrolled compared with private payers (0.71/1,000 vs. 2.03/1,000 in 2009) and males (1.26/1,000 vs. 1.81/1,000 in 2009) in all years. Overall utilization of epilepsy surgery remained low as the range in number of cases per year was 375 (1997) to 706 (2009). The majority of procedures took place at children's hospitals (range: 84 – 100%), and teaching hospitals (85 – 97%).

Conclusion: The rate of pediatric epilepsy surgery has increased, indicating increased awareness among health professionals of the benefits of early epilepsy surgery. However, surgery continues to be underutilized, especially among African-American children and those enrolled in Medicaid, indicating additional outreach efforts targeted toward general pediatricians, family medicine physicians and general neurologists may be needed to improve referral of difficult to treat epilepsy cases to specialized care.

Continuous EEG Monitoring (cVEEG) of Progressive Cerebral Edema in a Pediatric Patient

Authors: Bilal Zonjy, MD; Asim Shahid, MD; Ingrid Tuxhorn, MD

Background: We analysed (cEEG) changes in a pediatric intensive care patient with progressive cerebral edema. cEEG is routinely used in pediatric and adult intensive care units to detect and monitor the management of seizures and status epilepticus. cEEG is also sensitive to changes in intracerebral pressure, cerebral metabolism and cerebral ischemia. We report sequential changes in amplitudes, frequency, morphology and topography of EEG activity, documenting progression of cerebral edema in a pediatric patient.

Case Description: After a short diarrheal illness, a 14-month-old boy presented with lethargy, hypovolemic shock, hypernatremia and metabolic acidosis. He was resuscitated, intubated and treated with pressors and neuromuscular blockade. No clinical seizures were noted. The initial cEEG showed rhythmic high amplitude 2 – 3 Hz periodic waves over all brain regions. The initial computed tomography (CT) scan was normal. Within 12 hours, there was progressive flattening of the cEEG activity with loss of the periodic pattern. This event started in the parasagittal leads and extended into the temporal leads. The child deteriorated after resuscitation and died. Prior to death, the cEEG was very low amplitude throughout. The CT scan performed a few hours after the amplitude changes in the cEEG showed marked cytotoxic edema throughout the central semiovale and effacement of cisterns and sulci. The gradual loss of cEEG amplitudes and wave activity preceded neurologic deterioration by three to five hours.

Conclusion: cEEG is a well-established tool for monitoring seizures, status epilepticus, and changes in cerebral metabolism and perfusion. This case demonstrates that cEEG can monitor brain perfusion changes coupled with progressive cerebral edema. The coupled changes may precede the clinical deterioration and be helpful for earlier interventions. Our case demonstrated initial parasagittal loss of activity followed by temporal lobe changes and subsequent flattening throughout the EEG.

The Region's Highest-Quality Stroke Care

University Hospitals Case Medical Center is Northeast Ohio's *first* and *only* **Joint Commission-certified Comprehensive Stroke Center**, demonstrating our ability to treat the most complex cases with:

- The area's most experienced stroke care team
  - Specialist and neurosurgeon availability 24/7
- The most advanced diagnostic and treatment technologies
  - Gamma Knife® and CyberKnife®
- Beacon Gold Award-winning Neuroscience ICU
- A full continuum of stroke care from arrival through rehabilitation

To refer a patient or learn more, call 216-844-2427 or visit UHhospitals.org/strokecenter.

American Heart Association
American Stroke Association
CERTIFICATION
Meets standards for
Comprehensive Stroke Center

University Hospitals
Case Medical Center

Among the nation's leading academic medical centers, University Hospitals Case Medical Center is the primary affiliate of Case Western Reserve University School of Medicine, a nationally recognized leader in medical research and education.

UH Case Medical Center is the 2012 recipient of the American Hospital Association–McKesson Quest for Quality Prize.

Back inside cover intentionally blank

Presented by:

University Hospitals
Neurological Institute

Sponsored by:

School of Medicine
Case Western Reserve University

CME Information

Target Audience

This continuing medical education (CME) program is provided by Case Western Reserve University School of Medicine and is intended for all physicians, particularly neurologists and neurological surgeons, family practice and internal medicine physicians, interested in the latest advances in the management of neurological disorders.

Educational Objectives

Upon completion of this educational activity, the participant should be able to:

- Identify which patients benefit most from carotid endarterectomy vs. carotid stenting
- Review the best medical management for patients with intracranial atherosclerosis
- Understand the role of stenting for patients with intracranial stenosis
- Review current strategies for anticoagulation in the setting of atrial fibrillation
- Recognize how new brain imaging techniques can guide acute stroke therapy
- Identify which patients benefit most from intravenous thrombolytic therapy
- Understand the role of intra-arterial thrombolysis and thrombectomy in acute stroke therapy
- Understand the role of the combination of intravenous plus intra-arterial thrombolysis

Accreditation Statement

Case Western Reserve University School of Medicine is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Case Western Reserve University School of Medicine designates this enduring material for 2.0 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Release Date: June 15, 2013 Expiration Date: June 16, 2014

Disclosure Statement

The policy of the Case Western Reserve University School of Medicine CME Program requires that the Activity Director, planning committee members and all activity faculty (that is, anyone in a position to control the content of the education activity) disclose to the activity participants all relevant financial relationships with commercial interests. Where disclosures have been made, conflicts of interest, real or apparent, must be resolved. Disclosure will be made to activity participants prior to the commencement of the activity. The School of Medicine also requires that faculty make clinical recommendations based on the best available scientific evidence and that faculty identify any discussion of "off-label" or investigational use of pharmaceutical products or medical devices.

To Obtain *AMA PRA Category 1 Credits*™

- Read the article.
- Reflect on the content.
- Successfully complete the post-test located at **UHhospitals.org/NIJournalSummer2013**
- A grade of 100% is required for passage.
- Complete the evaluation.
- Print the certificate of credit for your records.

Your credits will be recorded by the Case Western Reserve University School of Medicine CME Program and made a part of your transcript. For more information, contact the CME program at medcme@case.edu.

Fee

There is no fee for this program.

Medical Disclaimer

Medicine is an ever-changing science. As new research and clinical experience broaden our knowledge, changes in treatment and drug therapy are required. The authors have checked with sources believed to be reliable in their efforts to provide information that is complete and generally in accord with the standards accepted at the time of publication.

Although every effort is made to ensure that this material is accurate and up-to-date, it is provided for the convenience of the user and should not be considered definitive. Neither the authors nor Case Western Reserve University School of Medicine nor any other party who has been involved in the preparation or publication of this work warrants that the information contained herein is in every respect accurate or complete, and they are not responsible for any errors or omissions or for the results obtained from the use of such information.

Learners are encouraged to confirm the information contained herein with other sources. This information should not be construed as personal medical advice and is not intended to replace medical advice offered by physicians. Case Western Reserve University School of Medicine will not be liable for any direct, indirect, consequential, special, exemplary, or other damages arising here from.

University Hospitals

With 150 locations throughout Northeast Ohio, University Hospitals serves the needs of patients through an integrated network of hospitals, outpatient centers and primary care physicians. At the core of our health system is University Hospitals Case Medical Center. The primary affiliate of Case Western Reserve University School of Medicine, University Hospitals Case Medical Center is home to some of the most prestigious clinical and research centers of excellence in the nation and the world, including cancer, pediatrics, women's health, orthopaedics and spine, radiology and radiation oncology, neurosurgery and neuroscience, cardiology and cardiovascular surgery, organ transplantation and human genetics. Its main campus includes the internationally celebrated UH Rainbow Babies & Children's Hospital, ranked among the top hospitals in the nation; UH MacDonald Women's Hospital, Ohio's only hospital for women; and UH Seidman Cancer Center, a part of the Case Comprehensive Cancer Center, which holds the nation's highest designation by the National Cancer Institute of Comprehensive Cancer Center.