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Clinical Spotlight: Hereditary Hemorrhagic Telangiectasia: the Georgia Health Sciences experience
Welcome to another edition of Neuroscience Outlook. In the clinical spotlight we highlight our institutional experience with Hereditary Hemorrhagic Telangiectasia (HHT), a hereditary disorder characterized by mucocutaneous telangiectasias, visceral and cerebral arteriovenous malformations, and epistaxis. We are one of only a handful of HHT centers of excellence in the US and worldwide. In the research spotlight we present collaborative research by Dr. Tsugio Seki (Department of Physiology) on a novel transgenic mouse model of central nervous system AVMs. In departmental news, one of our research faculty members has received an Outstanding Faculty award, four of our clinical faculty received Best Doctor citations, and our Administrative Director received third place in a Charity Dance competition. Our pituitary clinic which provides multidisciplinary care to patients is also described in this section. The accomplishments of our residents and faculty and our presentations and publications are also chronicled. We hope you enjoy our latest issue.

Cargill H. Alleyne, Jr., M.D.
Professor and Marshall Allen Distinguished Chair

**Department News**

**Faculty member receives an Outstanding Faculty Award**

Krishnan Dhandapani, Ph.D. won an Outstanding Faculty Award from the Georgia Health Sciences University Faculty Senate. Dr. Dhandapani previously won a Distinguished Faculty Basic Sciences Award for excellence in research last year.

**Four faculty members receive Best Doctor citation**

Cole Giller, M.D., S. Dion Macomson, M.D., John Vender, M.D. and Cargill H. Alleyne, Jr., M.D. were cited in the June/July 2012 edition of Augusta Magazine as four of the “Best Doctors in America”. This accolade is given to the top 5% of physicians as designated by peers.

**Pituitary clinic initiated**

The Pituitary Clinic was established to meet the complex needs of our rapidly growing population of patients with sellar and parasellar lesions such as pituitary tumors, craniopharyngiomas, meningiomas, Rathke’s cleft cysts and other neuroendocrinologic disorders. This multidisciplinary clinic provides single point of service access for patients to simplify care, increase patient access, and increase patient convenience while minimizing travel and confusion. Patients, in a single visit, can undergo their imaging, if required, and meet with the specialists appropriate for their care. All services required for treatment of these patients are available at GHSU including medical endocrinology, complex imaging, neurointerventional surgery (for petrosal sinus sampling or evaluation for embolization), minimally invasive surgery with 2-D and 3-D endoscopy, open cranial resection, external beam conformal radiotherapy, single session Gamma Knife stereotactic radiosurgery, and multisession radiosurgery with the Extend program. The GHSU Gamma Knife center is one of ten centers in the U.S. that has the Extend technology. With the Extend capability we can treat larger lesions or those closer to critical structures with lower risk.

The clinic is co-directed by Max Stachura, M.D. (Endocrinology) and John Vender, M.D. (Neurosurgery, Skull base surgery, Radiosurgery). The other participants in the clinic are Arturo Solares, M.D. (ENT Skull base surgery), Cargill Alleyne, M.D. (Neurosurgery, Skull base surgery, Radiosurgery, Interventional neuroradiology), Ramon Figueroa, M.D. (Neuroradiology), Scott Rahimi, M.D. (Interventional neuroradiology), and Dilip Thomas, M.D. (Neuro-ophthalmology).

**Administrative Director wins 3rd place in Charity Dance competition**

The Georgia Health Sciences Neuroscience Center was a sponsor of Dancing Stars, a new benefit for the Georgia chapter of the Alzheimer’s Association. This fundraising event took place in June and comprised of 10 celebrity dancers paired with 10 professional dancers. Our Administrative Director, Chris Bonham, and his professional dance partner won third place in the competition.

Chris Bonham and partner strike a pose.
Contributor Acknowledgement

We are deeply grateful to the Gardini family who donated to the department and to Dr. Betty Wray who contributed to the Marshall Allen Lectureship Endowment.

Clinical Spotlight

Hereditary Hemorrhagic Telangiectasia: the Georgia Health Sciences experience

Osler-Weber-Rendu disease or Hereditary Hemorrhagic Telangiectasia (HHT) is a hereditary disorder characterized by mucocutaneous telangiectasias, visceral arteriovenous malformations, and epistaxis. The prevalence of HHT has been estimated between 1 in 5,000 to 1-2 in 100,000. In some populations e.g. the Dutch, French and Japanese populations the prevalence may be as high as 5 in 8,000. HHT is linked to at least 5 genes on different chromosomes and is inherited in an autosomal dominant fashion with high penetrance and variable expressivity. By age 16, 71% of patients have developed at least one sign of HHT; by age 40 this number increases to greater than 90%.

HHT has been linked to numerous neurologic complications including cerebral arteriovenous malformations (AVMs), spinal AVMs, cerebral abscess, ischemic stroke, intracerebral hemorrhage, migraine headache, and seizures. Cerebral AVMs have been of particular interest in the HHT population as they have an increased frequency and can have potentially devastating consequences if untreated. Cerebral AVMs have been reported to occur in 10% of patients with HHT1 (Endoglin [ENG] deficiency), and 1% of patients with HHT2 (Activin-like kinase receptor 1[ACVRL, Alk-1] deficiency), compared to a rate of 1.1 to 10.3 per 100,000 (~0.1%) of AVMs in the general population.

Cerebral AVMs have a reported annual spontaneous hemorrhage rate of 3-4%, with potentially devastating consequences at the time of rupture. As such, current consensus guidelines recommend screening patients with possible or definite HHT for cerebral vascular malformations (CVMs) using MRI with and without contrast enhancement (including sequences to detect blood products in order to increase sensitivity). Debate exists in the literature regarding this recommendation, as some authors argue that cerebral AVMs in HHT have a different natural history and lower spontaneous rupture rate (as low as 0.36-0.56% per year) than in the general population.

At GHSU we have one of only thirteen HHT centers of excellence in the US and one of only 35 worldwide. Our center, directed by pulmonologist Dr. James Gossage, was established in November 2003 and is notable for its multidisciplinary approach with input from Pulmonology, Genetics, Interventional radiology, Gastroenterology, Otolaryngology, Neurosurgery and Neuroendovascular surgery. We are in the process of performing a retrospective review of prospectively collected data from a database of 372 patients seen in our HHT center. For control, 413 consecutively collected MRI examinations of the brain were reviewed for the presence of cerebral vascular malformations in a blinded fashion.

The goal of our study is to further characterize the types, frequency, and sequelae of CVM in the HHT patient population. This study differs from most prior studies in three ways. One, we screened for the full spectrum of CVM including cavernous malformations, capillary telangiectasias, developmental venous anomalies (DVAs), arteriovenous fistulas (AVF), and aneurysms; two, our patient population was screened for CVM using more powerful MRI magnets than prior studies (which were circa 2000); and three, we compared our HHT data to a contemporary control group of patients who had MRI examinations of the brain— as opposed to using historical controls. A better understanding of the cerebral vascular pathology in HHT patients should guide our diagnostic and treatment choices, and may also help us better understand the etiology of cerebral vascular malformations in general.
Clinical Spotlight (continued)

Clinical Case

The patient is an 11 year-old boy with HHT and with a family history of the same who upon screening was noted to have a complex arteriovenous fistula with and venous varix and venous outflow constriction (Figs 1-2). There was also retrograde cortical venous flow with a secondary venous varix indicative of a high risk of hemorrhage. He underwent endovascular occlusion of the fistula with detachable platinum coils. At the end of the procedure stasis was noted in the primary varix with non-filling of the secondary varix while still anticoagulated (Fig 3). The patient was discharged neurologically intact the day after embolization. A delayed angiogram showed complete occlusion of the lesion (Fig 4).

Figure 1 (a and b). T2-weighted MR shows AV fistula with venous varices.

Figure 2 (a and b). AP views of R. ICA injection shows AV fistula with venous varix and constricted venous outflow. A retrograde draining vein with a secondary varix is also noted.

Figure 2 (c and d). Lateral views of R. ICA injection showing the complex vascular lesion.

Figure 2e. AP view of L. ICA injection shows the complex vascular lesion.

Figure 3 (a and b). AP and lateral R. ICA injection shows coils at fistula.

Figure 4 (a and b). Delayed arteriogram shows complete resolution of the lesion.

M. Neil Woodall, M.D., Melissa McGettigan, M.D., Ramon Figueroa, M.D., James R. Gossage, M.D., and Cargill H. Alleyne, Jr., M.D.
Novel transgenic mouse model of central nervous system AVMs

The research reviewed in this section here was recently published in Stroke (Milton I, Ouyang D, Allen CJ, Yanasak NE, Gossage JR, Alleyne CH, Seki T: Age-dependent lethality in novel transgenic mouse models of central nervous system arteriovenous malformations. Stroke 43:1432-1435, 2012). A provisional patent application has been filed (US 61/479,382: Seki T, Yanasak N, Alleyne C; Mouse model of hemorrhagic arteriovenous malformation in neurological tissues)

Hemorrhage from central nervous system (CNS) arteriovenous malformations (AVMs) may cause severe neurological deficit or death. AVMs are currently treated expectantly or with surgical, endovascular, and/or radiosurgical obliteration. Limited research in development of therapeutic medications for AVM has been due, in a large part, to an absence of an appropriate animal model. Conventional and conditional Alk1 deletion mouse AVM models cause severe vascular malformations in diverse organs and lethal hemorrhages. Recently, an AVM model was developed by a viral vector-mediated simultaneous expression of vascular endothelial growth factor (VEGF) and Cre recombinase in activin receptor-like kinase 1 (Alk1; Acvrl1) conditional deletion mice but this model did not cause hemorrhage or neurological deficit.

Alk1 is predominantly expressed in arterial and pulmonary capillary endothelial cells (ECs) during development and plays a critical role in formation of a mature vascular network. In humans, a number of ALK1 gene mutations are identified in patients with an autosomal dominant inherited vascular disease, hereditary hemorrhagic telangiectasia (HHT), which is characterized by AVM formation in various organs including the brain and spinal cord.

Our novel AVM mouse models exhibit hemorrhage, paralysis, and partial lethality. The models were generated by conditionally deleting Alk1 gene with SM22-Cre transgene. All of these mice developed AVMs in their brains, and a majority of them died or were paralyzed due to internal hemorrhages before reaching 10 weeks of age. A subset of mice, however, survived more than one year carrying multiple AVMs (figures 1 and 2). In addition, we identified variegated expression of angiopoietin 2 (Agpt2) and a few inflammation related genes in the rupture-prone AVM walls. We believe these models can be an exceptional tool to study the pathophysiology of AVM hemorrhage.

Ian Milton, Dan Ouyang, M.D., Caitlin J. Allen, Nathan Yanasak, Ph.D., James R. Gossage, M.D., Tsugio Seki, M.D., Ph.D., Cargill H. Alleyne, Jr., M.D., and Tsugio Seki, M.D., Ph.D.

Facility Update and Staff Update

Accomplishments and recognition

Krishnan M. Dhandapani, Ph.D. was the recipient of an Outstanding Faculty Award from the Georgia Health Sciences University Faculty Senate. Dr. Dhandapani previously won a Distinguished Faculty Basic Sciences Award for excellence in research last year. He was also the recipient (with Dr. Alleyne co-PI) of an NIH R-21 award for “Therapeutic targeting of CD36 following intracerebral hemorrhage”. In addition, Dr. Dhandapani was co-Chair of the American Heart Association, Brain 2 Panel. He was also scientific and/or grant reviewer on multiple panels including the Department of Defense-Applied Neurotrauma Research – Applied/Clinical Sciences -2 Study Panel, the Department of Defense-Applied Neurotrauma Research – Clinical Sciences/Diagnostics and Therapeutics Development Study Panel, the American Heart Association – Western Affiliate Innovation Grant Award, the Veterans Affairs (VA) – Neurobiology A (NURA) Study Panel, and the NIH, Brain Injury and Neurovascular Pathology (BINP) Study Section.

Sergei Kirov, Ph.D. was a reviewer on an NIH Special Emphasis Panel “Synaptic Vesicles and Synaptogenesis”
Faculty Update and Staff Update (continued)

John Vender, M.D. was selected one of the Best Doctors in America.

Cole A. Giller, M.D., Ph.D., M.B.A. was selected one of the Best Doctors in America. In addition he was mentioned in an Augusta Chronicle article (February 27th) featuring one of his patients operated upon for head trauma. He was also included in newscast on Channel 12’s feature (February 15th) of one of his pediatric patients who underwent a deep brain stimulation procedure for dystonia (http://www.wrdw.com/home/headlines/Nine_year_old_Aiken_boy_able_to_walk_again_thanks_to_deep_brain_stimulation_139350548.html).

Cole A. Giller, M.D., Ph. D., MBA

Haroon F. Choudhri, M.D. was a moderator at the Plenary Session for Minimally Invasive Spine Surgery at the First Saudi International Spine Conference in Riyadh, Saudi Arabia in January. In addition he was an instructor at a Cadaver Workshop for Lateral Transpsoas Interbody Fusion (LTIF) at the Stryker Lateral Approach Course in May.

S. Dion Macomson, M.D. was selected one of the Best Doctors in America.

Residents’ Corner
Accomplishments and recognition

Patrick Youssef, M.D. was honored at our annual resident graduation ceremony in June. Dr. Youssef is currently completing an Endovascular fellowship in the Department of Neurosurgery at Emory.

Basheer Shakir, M.D. passed the written portion of the neurosurgical board examinations in March (during his PGY-4 year).

Dr. Patrick Youssef with faculty at his graduation

Douglas Hughes, M.D. was awarded the prize for Best Resident Presentation at the Spring meeting of the Georgia Neurosurgical Society meeting held in Amelia Island, Florida. His presentation was entitled “Experience with laparoscopic placement of peritoneal catheter in ventriculoperitoneal shunts at Children’s Medical Center, Medical College of Georgia 2007-2011”

This summer we welcomed our new PGY-1 resident Nathan Todnem, M.D. into our residency. Nathan graduated from University of Louisville, KY.

Presentations and Publications (January-June 2012)

Presentations:

Alleyne CH: Introduction to Neurosurgery. Surgery 5000 lecture series, Medical College of Georgia, GHSU, January 2012


Giller C: Surgery for Parkinson’s Disease. Parkinson’s Support Group, Columbia, SC, February 2012

Kirov SA: Cortical spreading depolarization: Emerging pathophysiologic mechanisms in the acutely injured brain. Vascular Biology
Presentations and Publications (January-June 2012) (continued)

Center, GHSU, Augusta, GA, February 2012

Vender JR: Common neurological tumors. Physicians Assistants’ lecture, School of Allied Health, GHSU, February 2012

Vender JR: Vestibular schwannoma. Masters of Otolaryngology Symposium, Medical College of Georgia, GHSU, February 2012

Alleyne CH: Neurovascular interventions for ischemic and hemorrhagic stroke. EMS Stroke conference, Medical College of Georgia, GHSU, March 2012

Dhandapani KM: Neuroimmune interactions after TBI: a role in the development of cerebral edema? Department of Neurobiology and Anatomy, Drexel College of Medicine, Philadelphia, PA, March 2012

Marshall R: Overcoming staff resistance to change, changing the view that family members are visitors, and applying patient- and family-centered care in the ICU. Institute for Patient- and Family-Centered Care, Emory Healthcare, Atlanta, GA, March 2012

Alleyne CH: Subarachnoid hemorrhage and unruptured intracranial aneurysms: Diagnosis and management. Comprehensive Stroke Management Update. Hilton Head, SC, April 2012

Vender JR: Malignant cerebral edema: from hyperventilation to hemicraniectomy, Comprehensive Stroke Management Update, Hilton Head, SC, April 2012

Alleyne CH: Introduction to Neurosurgery. Surgery 5000 lecture series, Medical College of Georgia, GHSU, April 2012


Wang DC, Rahimi S: Retrospective study of cranioplasty using dura ‘sandwich’ technique during decompression versus single layer dura substitute. American Association of Neurological Surgeons Meeting, Miami, FL, April 2012

Alleyne CH: Neurovascular interventions for ischemic and hemorrhagic stroke. GHSU Stroke conference, Medical College of Georgia, May 2012


Choudhri HF: Management of subaxial cervical spine trauma. 13th Dubai Spine Conference, Dubai, UAE, May 2012

Choudhri HF: Lateral transposas interbody fusion (LTIF) in degenerative spine disease. 13th Dubai Spine Conference, Dubai, UAE, May 2012

Choudhri HF: ARIA Tips & Tricks: Lateral transposas interbody fusion (LTIF) Stryker Lateral Approach Course, May 2012


Giller CA: EEG sonification for epilepsy surgery. 18th International Conference on Acoustic Display, Atlanta, Georgia, June 2012

Collins G, Hula H: Enhanced communication and collaboration through a patient- and family- centered care nurse residency. Patient- and Family- Centered Care Partners California Coalition, Long Beach, CA, June 2012


Publications:


Now available on Amazon.com and in bookstores!

Ned’s Head is the first in our series of educational children’s books. It presents facts about the human brain in an entertaining, colorful manner. The book consists of 16 verses in limerick form and they are masterfully illustrated by two seasoned professionals, one of whom who has previously illustrated 12 Curious George books.

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