

# JHN JOURNAL

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Predictors of Seizures  
Following Cranioplasty

Concurrent Metastatic Colon  
Adenocarcinoma and Vertebral  
Osteomyelitis: A Case Report

Hydrocephalus, A Complication  
of Flow-diversion?

Moyamoya: A Review of the  
Disease and Current Treatments

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Shunt Infection: Case Report and  
Review of the Literature

The ARUBA Trial: How Should We  
Manage Brain AVMs?



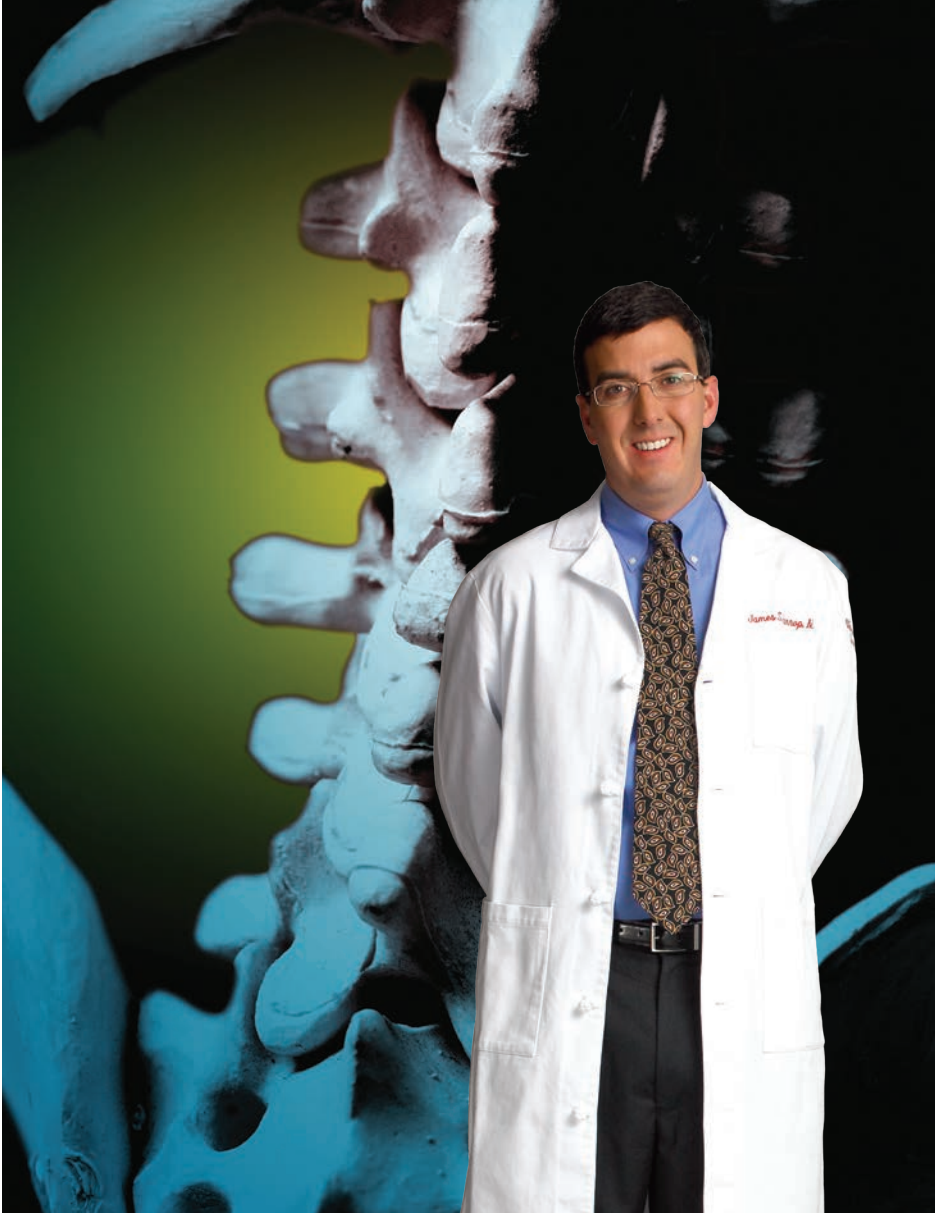
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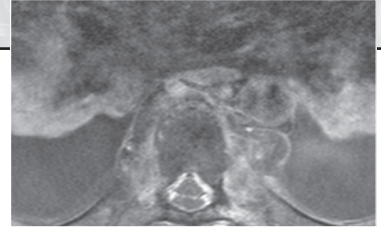
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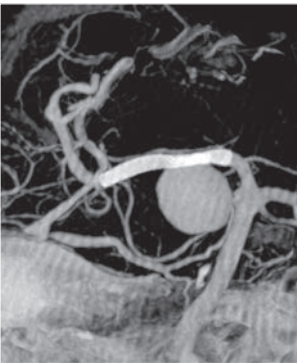
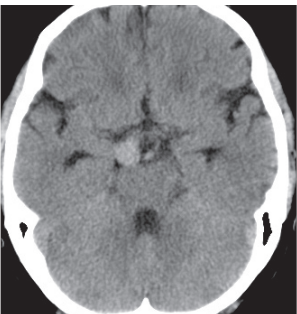
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# Predictors of Seizures Following Cranioplasty

Mario Zanaty, MD<sup>1</sup>; Nohra Chalouhi, MD<sup>1</sup>; Robert Rosenwasser, MD<sup>1</sup>; and Pascal Jabbour, MD<sup>1</sup>; Stavropoula Tjoumakaris, MD<sup>1</sup>

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## ABSTRACT

### Introduction

Seizures following cranioplasty are underreported and insufficiently investigated. Prevention of seizures has great potential to enhance the quality of life in cranioplasty patients. We aimed to identify specific risk factors related to the development of seizures in this setting.

### Methods

A retrospective review of the charts of all cranioplasty patients at a single institution from January 2000 to December 2011 was conducted. Patients who underwent craniectomy for cerebrovascular incidents, traumatic brain injury, non-traumatic subdural hematomas, and non-traumatic epidural hematomas were included, while patients who underwent craniectomy for tumors, infections, or epilepsy were excluded. We tested the following predictors of seizures: age, sex, race, diabetic status, hypertensive status, reason for craniectomy, urgency status of craniectomy (urgent vs. elective), location of cranioplasty, reoperation for hematoma, hydrocephalus post-cranioplasty, infection post-cranioplasty, and cranioplasty material type (autologous vs. synthetic). A multivariate logistic regression analysis was performed.

### Results

A total of 348 patients were included in the study with a mean age of 49.70 years. Of all patients in the study, 14.37% (50/348) had seizures after cranioplasty. Of these, only 4 patients (8.00% or 4/50) had a history of seizure prior to the cranioplasty. In a multivariate analysis, male gender, increasing age, and infection were associated with a higher risk of seizures. (OR=2.35 P<0.05; OR=1.04 P<0.05; OR=4.12 P<0.05: respectively). Trauma and convexity/bifrontal cranioplasty showed a trend of increased risk but were marginally significant (OR=2.86-P=0.06; OR=2.17 P=0.07, respectively).

### Conclusion

Cranioplasty seizures are predicted by male gender, older age, and history of infected cranioplasty. Similar to previous studies, the majority of seizures occurred in the post-cranioplasty period.

## INTRODUCTION

Seizures following cranioplasty remain underreported in the literature. Many of the patients who suffer from seizures after cranioplasty progress to develop epilepsy.<sup>1</sup> Prevention of seizures and, subsequently, of epilepsy can enhance the quality of life and neurological outcomes in those who have undergone this type of surgery.<sup>2</sup> Therefore, we aim to identify specific risk factors related to the development of post cranioplasty seizure.

## METHOD

### Design

The University Institutional Review Board approved the study protocol. We conducted a retrospective review of all patients who underwent cranioplasty at our institution from January 2000 to December 2011. The study included all patients who underwent a craniectomy for traumatic brain injury (TBI), non-traumatic subdural hematoma, non-traumatic epidural hematoma, hemorrhagic stroke, ischemic stroke, and subarachnoid hemorrhage (SAH). Patients who had undergone craniectomy for epilepsy were excluded. We found 348 patients to be eligible for the study.

### Study variables

We included in our study the following variables: age, sex, race, diabetic status, hypertensive status, tobacco use, reason for craniectomy, urgency status of craniectomy (urgent vs. elective), location of cranioplasty (unilateral convexity, bilateral convexity, bifrontal, and suboccipital), reoperation for hematoma, hydrocephalus post-cranioplasty, infection post-cranioplasty, and cranioplasty graft (synthetic vs. autologous bone graft). We ensured that only convincing epileptic events were included, therefore only documented seizures were included in the study. When in doubt, we reviewed the EEG and the neurology consult if ordered. Undocumented or unconfirmed seizures were excluded from the study. We also defined a previous history of seizure as one or more episodes of seizure prior to cranioplasty.

### Statistic Analysis

Data are presented as mean and range for continuous variables, and as frequency for categorical variables. Analysis was carried out using unpaired t-test, Chi-square, and Fisher's exact tests as appropriate. Univariate analysis was used to test covariates

predictive of seizure following cranioplasty. Interaction and confounding was assessed through stratification and relevant expansion covariates. Factors predictive in univariate analysis ( $p < 0.15$ )<sup>3</sup> were entered into a multivariate logistic regression analysis. P-values of  $\leq 0.05$  were considered statistically significant. Statistical analysis was carried out with Stata 10.0 (College Station, TX).

## RESULTS

### Demographics

A total of 348 patients met the study criteria. Data analysis revealed a mean age of 49.70 +/- 13.40 years. As for gender, 50.57% (176/348) of the patients were males and 49.43% (172/348) were females. The proportion of smokers was 46.84% (163/348) and that of non-smokers was 53.16% (185/348). Demographics and comorbidities are included in Table 1. The leading cause of craniotomy was SAH (52.01%), followed by TBI (18.96%), hemorrhagic stroke (16.09%), and ischemic stroke (10.92%). There were limited cases of non-traumatic subdural and

epidural hematoma (2.01%). The rate of reoperation for hematoma was 6.90%.

### Predictors of seizures

Post-cranioplasty seizure occurred in 14% (50/348) of the patients. Of these, only 4 patients (8.00% or 4/50) had a history of seizure prior to their cranioplasty.

Univariate analysis (Table 2) revealed the following variables to be associated with a higher risk of post-cranioplasty seizure: male gender (OR = 2.37,  $P < 0.05$ ), older age of more than 60 years (OR = 1.02,  $P < 0.05$ ), bifrontal and convexity cranioplasty location when compared to suboccipital (OR = 9.43,  $P < 0.05$ ), decompressive hemicraniectomy (DHC) for trauma (OR = 3.22,  $P < 0.05$ ), cranioplasty site infection (OR = 4.54,  $P < 0.05$ ), and reoperation for hematoma evacuation (OR = 3.40,  $P < 0.05$ ). Smoking, hypertension, diabetes, and race did not reach statistical significance ( $p > 0.05$ ) (Table 2). There was no difference in seizure rate between patients who had a synthetic graft and those who had an autologous bone graft (Table 2).

In a multivariate analysis (Table 3), male gender, increasing age, and infection were predictive of seizures (OR = 2.35  $P < 0.05$ ; OR = 1.04  $P < 0.05$ ; OR = 4.12  $P < 0.05$ ; respectively). Trauma and cranioplasty location showed a trend of increased risk but did not achieve statistical significance (OR = 2.86  $P = 0.06$ ; OR = 2.17  $P = 0.07$ , respectively).

**Table 3: Multivariate analysis**

Variable	OR (P-value)
Male gender	OR=2.35 P<0.05
Increasing age	OR=1.04 P<0.05
Infection	OR=4.12 P<0.05
Trauma	OR=2.17 P=0.07
Bifrontal/convex	OR=2.86 P=0.06

## DISCUSSION

### Background

Seizures post-cranioplasty can be attributed to the underlying etiology, the DHC, or the cranioplasty itself. It is not uncommon to have a minimal amount of brain tissue manipulation during cranioplasty. This manipulation may precipitate seizure activity in an already susceptible brain tissue<sup>4</sup> and may independently contribute to post-operative seizure<sup>5</sup>. In a recent retrospective study, cranioplasty was an independent risk factor for seizures occurrence in patients undergoing decompressive hemicraniectomy (DHC) for stroke or trauma.<sup>1,4</sup> The authors noted that the majority of seizures occurred in the following weeks after cranioplasty for patients who underwent DHC for middle cerebral artery stroke<sup>1</sup>. Free radical formation, ionic balance disturbance, and cerebral manipulation have been postulated as a mechanism of post-operative seizure formation.<sup>5,6</sup> The primary objective of our study was to evaluate the influence of specific variables on the seizures' rate after cranioplasty.

### Demographic risk factors and comorbidities

We found that male gender and increasing age were the only demographic variables associated with a higher risk of seizure. Similarly, Creutzfeldt et al. found that seizures were more common in males.<sup>1</sup> None of the continuous variables in their study, which included age, Glasgow coma scale and National Institute of Health Stroke Scale, was associated with

**Table 1: Demographics and comorbidities**

Demographics/comorbidities	Proportions or Mean
Age	49.70 +/- 13.40
Gender	Males: 0.51; Females: 0.49
Race	Caucasian = 0.73; African-American = 0.16; Hispanic = 0.07; Asian = 0.04
Smoking	Smokers = 0.47; Non-Smoker = 0.53
Diabetic	Diabetic = 0.15; Non-Diabetic = 0.85
Blood Pressure	Hypertensive = 0.57; Normotensive = 0.43

**Table 2: Univariate analysis**

Risk Factors	Odds Ratio, P value
Male gender	OR=2.37, P<0.05
Older age	OR=1.02, P<0.05
Bifrontal/convexity cranioplasty location	OR=9.43, P<0.05
Craniectomy for trauma	OR=3.22, P<0.05
Cranioplasty site infection	OR=4.54, P<0.05
Reoperation for hematoma	OR=3.40, P<0.05
Diabetes mellitus	OR=1.66, P=0.19
Hypertension	OR=1.03, P=0.911
Synthetic material	OR=0.94, P=0.85

seizure occurrence. We have no explanation to why male gender increases the seizure rate, but it appears that a moderate preponderance of males exists in most reports of first adult seizures<sup>7-10</sup>. However in these reports, statistical significance was not evaluated. Race, smoking and hypertension had no effect on the outcome in our study. The finding of higher seizure rate in older age is consistent with previous studies that have shown age to affect the risk of epilepsy, with young children (<1 year) and older patients (> 65 years) having the highest incidence.<sup>11</sup> Other studies have also reported that younger age predisposes to seizures following DHC for malignant stroke.<sup>2</sup> In our study, both male gender and increasing age remained significant in multivariate analysis (Table 2).

### Underlying etiology as a predictor of seizure

Post-traumatic epilepsy is known to occur in patients with extensive traumatic brain injury (TBI). Brain tissue damage leads to toxic neurotransmitter secretion that may result in excessive neuronal stimulation and early post-traumatic seizure formation.<sup>12</sup> When extensive damage occurs, iron accumulation in the tissue undergoes a chain of oxidoreduction reactions that generates bioactive free radicals.<sup>12,13</sup> This is believed to lead to the formation of epileptic foci responsible for late epilepsy.<sup>6,12</sup> Earlier studies argued that cranioplasty might decrease the risk of post-traumatic epilepsy,<sup>14-18</sup> but when groups with similar injury were compared, no significant statistical differences were noted in the seizure rates related to the cranioplasty itself.<sup>14</sup> We found that seizures were more common in trauma patients and in those who underwent bifrontal or convexity cranioplasty when compared

to suboccipital location. However, trauma and cranioplasty location did not achieve statistical significance when multivariate analysis was applied (OR=2.86 P=0.06 for trauma and OR=2.17 P=0.07 for location). Other reasons for craniectomy included in the study were stroke, SAH, and non-traumatic epidural and subdural hematomas, none of which conferred a higher risk of seizure. It is noteworthy that the caseload of non-traumatic subdural and epidural hematomas was not large enough to yield a firm analysis. Lee et al. reviewed the charts of 243 cranioplasties and found that 14.81% of patients had a post-cranioplasty seizure, rendering it the most common complication in their study<sup>6</sup>. In their report, the three statistically significant predictors were TBI, DHC for hemorrhagic stroke, and neurological deficit before cranioplasty. Their model explained 9.1% (Cox and Snell R square) in the variance of factors leading to seizures.

### Cranioplasty complications as predictors of seizure

Complications of cranioplasty, such as infections and reoperation for hematoma, were associated with post cranioplasty seizures development. Reoperation for hematoma combines the risk of the surgery's free radical formation with the iron supply of blood, which might explain the higher rates of seizure in this cohort of patients. However, in multivariate analysis, infection was the only cranioplasty complication that predicted seizures.

We had a similar or a slightly lower proportion of seizures in our study when compared with the literature (Table 4), although the data necessary for a head-to-head comparison is not available. The seizure rate was strikingly high in some studies on DHC for middle

cerebral artery infarction (Table 4). Of these, only one study by Creutzfeldt and colleagues, reported on the time of seizure occurrence relatively to the cranioplasty operation, and found as we previously discussed, that most of the seizures occurred within the weeks following cranioplasty.<sup>1</sup> Creutzfeldt et al estimated the 1-year risk of seizure, using Kaplan-Meier method, to be 57%; remarkably higher than the risk reported by previous craniectomy studies, which ranged between 3-40%.<sup>1,2,4,6,19,20</sup> The authors attributed the elevated risk to the younger age of their cohort, the malignancy of the patients' stroke and the long-term follow-up.

### Limitation

The main limitation is the retrospective design of the study. It is also difficult to differentiate whether the risk of seizure was due to the initial injury, or to a combination of both the cranioplasty and the etiology. It would be difficult to answer this question because the control group required must not undergo DHC. However, this was not the purpose of our study. Finally, some patients might have had seizures after their last follow-up but were not treated in our institution. Nevertheless, our model explains 15.3% (pseudo R square) in the variance of factors leading to post-cranioplasty seizures.

### CONCLUSION

In conclusion, male gender, cranioplasty infection and older age were significantly associated with seizures. Diabetes mellitus, hypertension, smoking, race, SAH, ischemic/hemorrhagic stroke, subdural/epidural hematoma, reoperation for hematoma, and post cranioplasty hydrocephalus did not affect the risk for developing seizures. Prospective studies are needed to confirm these results and perhaps set protocols that might decrease the rate of complication.

**Table 4: Seizure rate after cranioplasty and DHC**

Seizure rate after cranioplasty	
Walcot et al 4	3.35%
Sobani et al <sup>20</sup>	15.6%
Lee et al <sup>6</sup>	14.81%
Seizure rate after Decompressive Hemicraniectomy	
Creutzfeldt et al <sup>1</sup>	49%*
DECIMAL** trial <sup>19</sup>	40%
* Most of the seizures occurred in the weeks following cranioplasty	
**DECIMAL = DEcompressive Craniectomy in MAlignant MCA Stroke	

## REFERENCES

1. Creutzfeldt CJ, Tirschwell DL, Kim LJ et al. Seizures after decompressive hemicraniectomy for ischaemic stroke. *Journal of neurology, neurosurgery, and psychiatry* 2013.
2. Macdonald RL. Seizures after craniectomy: an under-recognised complication? *Journal of neurology, neurosurgery, and psychiatry* 2013.
3. Altman DG. Practical statistics for medical research. Boca Raton, Fla.: Chapman & Hall/ CRC 1999.
4. Walcott BP, Kwon CS, Sheth SA et al. Predictors of cranioplasty complications in stroke and trauma patients. *Journal of neurosurgery* 2013; 118: 757-62.
5. Honeybul S. Complications of decompressive craniectomy for head injury. *J Clin Neurosci* 2010; 17(4): 430-5.
6. Lee L, Ker J, Quah BL et al. A retrospective analysis and review of an institution's experience with the complications of cranioplasty. *Br J Neurosurg* 2013; 27: 629-35.
7. Hopkins A, Garman A, C CC. The first seizure in adult life. Value of clinical features, electroencephalography, and computerised tomographic scanning in prediction of seizure recurrence. *Lancet* 1988; 1(8588): 721-6.
8. van Donselaar C, Schimsheimer RJ, Geerts AT, Declerck AC. Value of the electroencephalogram in adult patients with untreated idiopathic first seizures. *Arch Neurol* 1992; 49(3): 231-7.
9. Musicco M, Beghi E, Solari A, Viani F. Treatment of first tonic-clonic seizure does not improve the prognosis of epilepsy. First Seizure Trial Group (FIRST Group). *Neurology* 1997; 49(4): 991-8.
10. King MA, Newton MR, Jackson GD et al. Epileptology of the first-seizure presentation: a clinical, electroencephalographic, and magnetic resonance imaging study of 300 consecutive patients. *Lancet* 1998; 352(1933): 1007-11.
11. Hauser WA, Annegers JF, Kurland LT. Incidence of epilepsy and unprovoked seizures in Rochester, Minnesota: 1935-1984. *Epilepsia* 1993; 34(3): 453-58.
12. Khan A, Banerjee A. The role of prophylactic anticonvulsants in moderate to severe head injury. *Int J Emerg Med* 2010; 3: 187-91.
13. McCord JM. Iron, free radicals, and oxidative injury. *J Nutr* 2004; 134(11): 3171S-2S.
14. Rish BL, Dillon JD, Meirowsky AM et al. Cranioplasty: a review of 1030 cases of penetrating head injury. *Neurosurgery* 1979; 4(5): 381-5.
15. Gilmour CH. Cranioplasty. *Can Med Assoc J* 1919; 9(10): 922-6.
16. Weiford EC, GARDNER WJ. Tantalum cranioplasty; review of 106 cases in civilian practice. *Journal of neurosurgery* 1949; 6(1): 13-32.
17. Woodhall B, Spurling RG. Tantalum Cranioplasty for War Wounds of the Skull. *Ann Surg* 1945; 121(5): 649-68.
18. Wolf JI, Walker AE. Cranioplasty: Collective review. *IntAbstrSurg* 1945; 81: 1-23.
19. Vahedi K, Hofmeijer J, Juettler E et al. Early decompressive surgery in malignant infarction of the middle cerebral artery: a pooled analysis of three randomised controlled trials. *Lancet Neurol* 2007; 6(3): 215-22.
20. Sobani ZA, Shamim MS, Zafar SN et al. Cranioplasty after decompressive craniectomy: An institutional audit and analysis of factors related to complications. *Surgical neurology international* 2011; 2: 123.

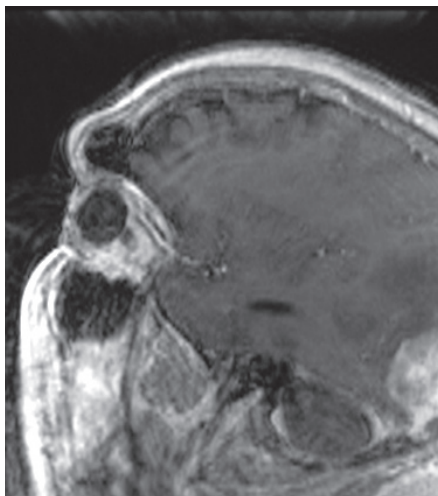


# Concurrent Metastatic Colon Adenocarcinoma and Vertebral Osteomyelitis: A Case Report

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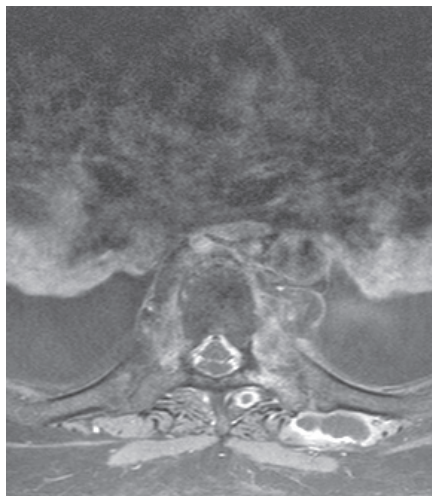
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**Image 1.**

MRI of the brain with gadolinium revealed a left occipital enhancing fusiform mass invading the skull, epidural and subdural space.



**Image 2.**

T2-weighted MRI with gadolinium, axial view, demonstrating a lesion within the thoracic spine at T7 with air within the vertebral body.

## Imaging

Imaging revealed significant findings in the abdomen, brain, and spine. CT of the abdomen revealed a sigmoid mass suggestive of colon cancer. CT of the brain revealed edema in the left temporooccipital region. Subsequent MRI of the brain with gadolinium revealed a left occipital enhancing fusiform mass invading the skull, epidural and subdural space. Imaging characteristics were most consistent with a metastasis (Image 1). CT imaging of the spine demonstrated a lesion within the thoracic spine at T7 with air within the vertebral body (Image 2). The pattern of intraosseous gas was concerning for gas-forming infection. Metastatic disease has also been described as a rare cause of intravertebral gas. The patient was further evaluated with MRI of Cervical, Thoracic and Lumbar Spine, which demonstrated enhancement at multiple levels, as well as loculated ventral and dorsal epidural collections, between T4 and T9 with T7 vertebral body enhancement, suggestive of infection (Images 3 and 4).

## INTRODUCTION

Vertebral osteomyelitis and metastases can have a similar presentation. In both entities, signs and symptoms can be subtle, such as fatigue, low-grade fevers and back pain. Non-invasive modalities such as laboratory studies and imaging play a critical role in helping narrow the diagnosis. In many cases however, it is not until a surgical specimen is obtained that a definitive diagnosis can be made. We present a patient who interestingly had both vertebral osteomyelitis and metastases in the same vertebral body.

## CASE REPORT

### Presentation

The patient is a 57-year-old man without significant past medical history who presented to a local emergency department with mental status change for several days. As reported by his family, history and physical exam revealed that the patient had been experiencing low back pain, dark and tarry stools, in addition to change in sensorium.

### Operative Management

The patient first underwent an image-guided left temporal craniotomy and tumor resection. After recovering from his first operation without complication he was discharged from the hospital. On second admission 3 weeks later, the patient was taken to the operating room for two separate staged spine surgeries. The first operation consisted of a left thoracotomy and T7 corpectomy and T6-8 arthodesis with an autologous iliac crest bone graft. Next, the patient underwent posterior exposure of the thoracic spine, laminectomy of T4-T9



with evacuation of epidural abscess, and irrigation and debridement of paraspinal abscess.

### Pathology

Pathology confirmed metastatic disease to the brain and spine at the level of T7 vertebral body consistent with adenocarcinoma with Signet ring cell features and concurrent osteomyelitis. Final culture from epidural abscess and T7 vertebral body was positive for anaerobic organism *Bacteroides fragilis*.

### Discussion

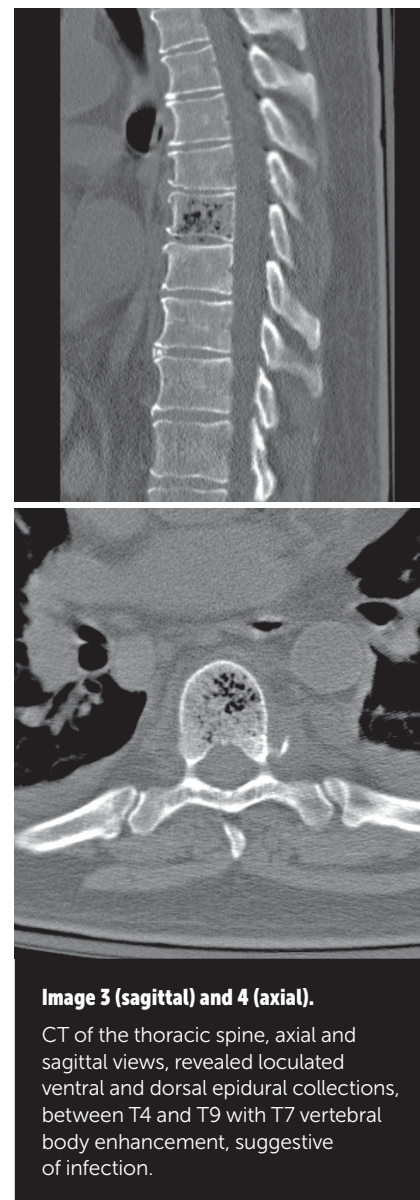
Vertebral osteomyelitis is part of a spectrum of spinal infections that has an incidence estimated at 2.4 cases per 100,000 populations.<sup>1</sup> The incidence is higher in older individuals: 6.5 cases per 100,000 among people over age 70 compared to 0.3 cases per 100,000 among people under age 20.<sup>1</sup> The mortality for vertebral osteomyelitis ranges from 2-20% and high rates of morbidity exist among survivors.<sup>2</sup> *Staphylococcus aureus*, seen in 55-90% of cases, is the most common causative agent in pyogenic vertebral osteomyelitis.<sup>1,3,4</sup> Complications of vertebral osteomyelitis can include direct seeding of other compartments leading to paravertebral, epidural, or psoas abscesses.<sup>1</sup> Patients with vertebral osteomyelitis commonly present initially with back pain.<sup>1,2</sup> The infection site determines where the patient will experience pain, with the lumbar spine being the most common site (58%).<sup>1,4</sup> Some patients will present with various neurologic deficits such as sensory loss, lower extremity weakness, paraplegia and radiculopathy.<sup>1,4</sup> Vertebral osteomyelitis can exist as an acute (occurring over a few days or weeks) or chronic process (lasting for weeks or months).<sup>1</sup> Patients undergoing a chronic process may complain of persistent back pain occurring over months to years as well as fever, malaise, anorexia, spinal tenderness, and rigidity.<sup>4</sup> Most cases of vertebral osteomyelitis are due to hematogenous seeding of a distant infection and consequently the symptoms of primary infection can dominate the signs of vertebral osteomyelitis.<sup>1</sup> In about half of all cases the source of infection is found.<sup>5</sup>

Laboratory findings of patients with vertebral osteomyelitis depend on the grade of the pathologic process and the causative agent.<sup>4</sup> Elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are highly sensitive laboratory findings for vertebral osteomyelitis with elevated values present in 98% and 100% of patients respectively. Comparatively, a high white blood cell (WBC) count or an increased neutrophil count on differential have low sensitivity.<sup>1</sup> Blood cultures are also necessary in the assessment of vertebral osteomyelitis.

The initial imaging study for vertebral osteomyelitis is usually plain radiography. The sensitivity and specificity of plain radiographs is very low. Additionally, plain radiographs will usually not detect early findings of the disease.<sup>1,4</sup> The earliest sign on plain radiography is a loss of definition and irregularity of the vertebral end plate usually starting anterosuperiorly. As the disease progresses the end plate becomes poorly defined and there is a decrease in disc height. Eventually there is sclerosis, osteophytosis, kyphotic deformity, and bony ankylosis.<sup>4</sup>

Magnetic resonance imaging (MRI) should be the initial choice for imaging in patients with neurologic impairment.<sup>1</sup> MRI is the method of choice and has a high accuracy (90%) for diagnosing vertebral osteomyelitis.<sup>1,2,4</sup> On T2-weighted sequences it shows a high intensity signal within the disc and loss of the intranuclear cleft. It is common for the disc space and two adjacent vertebral bodies to show involvement.<sup>1</sup> T1-weighted images are useful for disc material and bone differentiation. T1-weighted sequences reliably show specific signs of vertebral infection: low signal areas of the vertebral body, loss of definition of the end plates and interruption of the cortical continuity, and destruction of the cortical margins.<sup>4</sup>

Computed tomography (CT) has a lower sensitivity compared to MRI and has therefore a minor role in diagnosing early vertebral osteomyelitis.<sup>4</sup> CT can be helpful for assessing the status of the vertebral endplates, and is indicated for patients who are ineligible for MRI or to guide a percutaneous biopsy or for surgical planning.



**Image 3 (sagittal) and 4 (axial).**

CT of the thoracic spine, axial and sagittal views, revealed loculated ventral and dorsal epidural collections, between T4 and T9 with T7 vertebral body enhancement, suggestive of infection.

Vertebral metastases can be difficult to differentiate from vertebral osteomyelitis on patient presentation alone. Vertebral metastases occur in up to 90% of systemic cancer patients at time of death and about 30% of systemic cancer patients experience symptomatic vertebral metastases.<sup>6</sup> Vertebral metastases have the highest incidence in the 40-65 years old male population. The solid tumors that have the highest predilection for vertebral metastases are breast, lung and prostate.<sup>6,7</sup> The primary tumor most commonly spreads by the hematogenous

route to the vertebrae, invading the thoracic spine in 70% of symptomatic lesions, compared to 20% in the lumbosacral spine, and 10% in the cervical region.<sup>6</sup> In metastatic disease the most common site of neoplasm is the vertebral body and pedicle. The neoplasm can spread into the extradural space potentially leading to compression of the spinal cord, cauda equina, or nerve roots.<sup>8</sup>

Patients with vertebral metastases most commonly present with pain as their initial symptom (90% of patients). The pain is local, radicular, or mechanical. Pain does not improve with rest and lasts longer than six weeks. Patients may also have decreased muscle strength, sensitivity alterations, reduced anal sphincter tone, and loss of appetite.<sup>9</sup>

The first imaging technique historically utilized to diagnosis vertebral metastases is a plain radiograph of the spinal column. In order to detect radiographic changes 30-50% of trabecular bone needs to be destroyed. This is why early metastatic lesions may not be identified. The first radiographic change due to metastases is absence of the pedicle in the anterior-posterior view.<sup>9</sup> Radiographs also show bone destruction and sclerosis.<sup>8</sup> CT evaluates the bone architecture. MRI is superior to a CT in evaluating the structures surrounding the bone such as the muscles, ligaments, spinal cord, and extent of the neoplasm.<sup>6</sup> Thus, due to the soft tissue evaluation capabilities of

the MRI, the MRI is the imaging technique preferred in evaluating vertebral metastases. Furthermore, an MRI is 97% specific and 93% sensitive for the diagnosis of medullary compressions.<sup>9</sup>

Patients with vertebral osteomyelitis can have a similar presentation to patients with vertebral metastases. Both can experience chronic pain and neurologic deficits. Imaging techniques that unveil characteristic pathologic findings can help differentiate between the two entities. One difference between osteomyelitis and metastatic lesions of the vertebrae is that metastatic lesions do not destroy the intervertebral disc whereas osteomyelitis typically destroys the intervertebral disc and adjacent vertebral plateaus.<sup>6</sup> Patients with vertebral osteomyelitis tend to have involvement of their lumbar vertebrae whereas metastases have a predilection for the thoracic vertebrae. In addition to using imaging techniques to look for changes consistent with the suspected disease process, a blood culture and bone biopsy provide valuable information.<sup>1</sup> The University of Miami School of Medicine has described three patients with the same finding as our patient in this case: concomitant infection and tumor at the same level of the vertebral column. They emphasize that it is important to be able to differentiate between the two pathological conditions and thus make a correct diagnosis because the treatment of each is different.<sup>10</sup>

## REFERENCES

1. Zimmerli W. Clinical practice. Vertebral osteomyelitis. *N Engl J Med*. 2010;362:1022-1029.
2. Dunbar JA, Sandoe JA, Rao AS, Crimmins DW, Baig W, Rankine JJ. The MRI appearances of early vertebral osteomyelitis and discitis. *Clin Radiol*. 2010;65:974-981.
3. Hong SH, Choi JY, Lee JW, Kim NR, Choi JA, Kang HS. MR imaging assessment of the spine: infection or an imitation? *Radiographics*. 2009;29:599-612.
4. Tali E.T. Spinal infections. *Eur J Radiol*. 2004;50:120-133.
5. Mylona E, Samarkos M, Kakalou E, Fanourgiakis P, Skoutelis A. Pyogenic vertebral osteomyelitis: a systematic review of clinical characteristics. *Semin Arthritis Rheum* 2009;39:10-7.
6. Sciubba DM, Petteys RJ, Dekutoski MB, Fisher CG, Fehlings MG, Ondra SL, et al. Diagnosis and management of metastatic spine disease. *J Neurosurg Spine*. 2010.13(1):94-108.
7. Schuster, JM, Grady MS. Medical management and adjuvant therapies in spinal metastatic disease. *Neurosurg Focus*. 2001;11(6):e3.
8. Abdi S, Adams CI, Foweraker KL, O'Connor A. Metastatic spinal cord syndromes: imaging appearances and treatment planning. *Clin Radiol*. 2005;60(6):637-47.
9. Araujo JL, Veiga JC, Figueiredo EG, Barboza VR, Daniel JW, Panagopoulos AT. Management of metastatic spinal column neoplasms--an update. *Rev Col Bras Cir*. 2013.40(6):508-14.
10. Eismont FJ, Green BA, Brown MD, Ghandur-Mnaymneh L. Coexistent infection and tumour of the spine: A report of three cases. *J Bone Joint Surg*. 1987;69A:452-457.

# Hydrocephalus, a Complication of Flow-diversion?

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## INTRODUCTION

The pipeline embolization device (PED; Covidien/ev3, Irvine, CA) utilizes the principle of flow diversion and seeks to restore normal arterial anatomy for the treatment of brain aneurysms.<sup>1</sup> Globally, the neurovascular community has frequently used PED since 2008 with encouraging outcomes. Multiple case series have reported 6-month aneurysm obliteration rates of more than 80% and 1-year aneurysm obliteration rates of more than 90%.<sup>2-7</sup> Additional complications are being reported as the PED is being used to treat a greater number of patients and more diverse types of cerebral aneurysms.<sup>7-10</sup> Here we report the first case of a patient developing normal pressure hydrocephalus (NPH) after she was treated with the PED and discuss the management challenges of this complication.

## CASE REPORT

### Presentation to treatment

A 75-year old female was referred from an outside hospital for the management of an aneurysm found on MRA done for the work-up of a right third nerve and a partial sixth nerve palsy. On admission the patient had nausea, diplopia, and a significant headache that corresponded to 7/10 on the visual analogue scale. On neurological examination, right-sided third nerve and sixth nerve palsy were documented. A CT scan was performed to rule out hemorrhage, which showed a hyperdense mass (Figure 1) compatible with the aneurysm noted on an outside MRA. Age related cerebral atrophic and microangiopathic changes were also noted (Figure 2). The MRA showed a possible right posterior-communicating artery (PCOM) aneurysm. Digital Subtraction Angiography (DSA) showed a right-sided large, wide-neck P1-P2 aneurysm measuring 11 x 12 mm (Figure 3a). The patient was treated by embolization with a PED (2.5 x 16 mm). A dyna CT showed adequate placement of the PED (Figure 3b).

### Clinical and Radiological follow up

A follow-up angiogram was performed the next day and showed 50% thrombosis of the aneurysm with normal flow in the parent vessel (Figure 3c). The patient was discharged in stable condition the following day. The patient was kept on dual antiplatelet therapy (DAPT) consisting of aspirin (81mg) and clopidogrel (75mg).

Two months after PED deployment, the patient was complaining of persistent headaches and chronic third-nerve palsy. An MRI was ordered and was unchanged from baseline. An angiogram showed 100% thrombosis of the aneurysm (Figure 3d). The patient was prescribed steroids and was asked to follow up in clinics.

Two weeks later the patient started having difficulty ambulating, with shuffling gait and was even unable to walk on her own, in addition she was complaining of urinary

incontinence and worsening short-term memory loss. A head CT scan was performed (Figure 4), and showed mild increase in size of the ventricles compared to the immediate post-operative CT. A high-volume lumbar tap was performed, which showed significant improvement of her walk compared to the pre lumbar tap, as evaluated objectively by physical therapy. Therefore, the patient was diagnosed with NPH and the decision was made to shunt her.

### Management for NPH

The patient was maintained on 81mg of aspirin while clopidogrel was discontinued for 5 days. The risks of thromboembolic complications from discontinuing clopidogrel as well the risks of hemorrhagic complications during surgery were discussed with the patient and she underwent a standard ventriculoperitoneal shunt placement (Figure 5). The post-op CT scan showed a small amount of intra ventricular hemorrhage without any clinical significance. She recovered from surgery without any complications and was discharged home after three days in stable condition. She was kept on 81mg of aspirin and Plavix was restarted 48 hours post-operatively.

On 2-month follow up visit, the patient was walking independently without any shuffling, she was no more having any urinary problems and her short memory was still improving slowly.

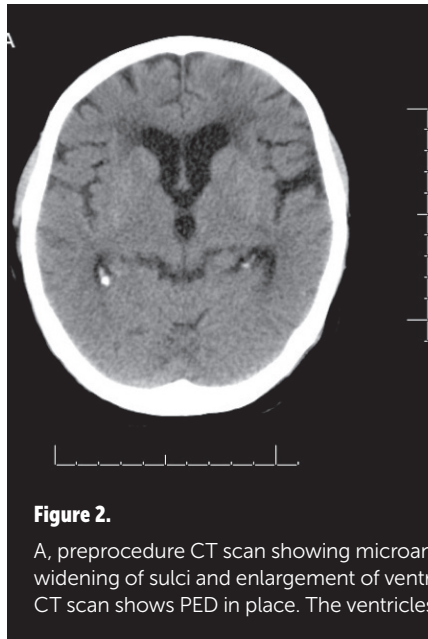
## DISCUSSION

In 2011, the PED was approved by the FDA for treatment of large and wide neck aneurysms of the internal carotid artery from the petrous apex to the superior hypophyseal artery on the basis of "Pipeline for Uncoilable or Failed Aneurysms study" (PUFS).<sup>5,7</sup> PED is generally associated with lower incidence of mortality and morbidity. According to a literature review by Tse et al, morbidity and mortality range between 4.5-16.6%

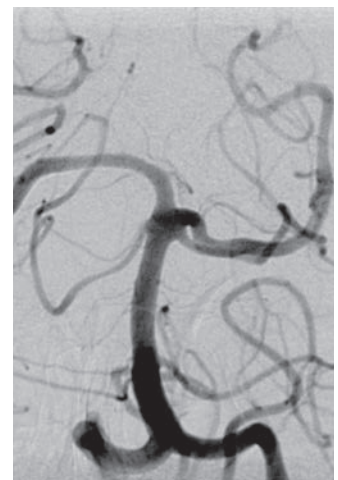
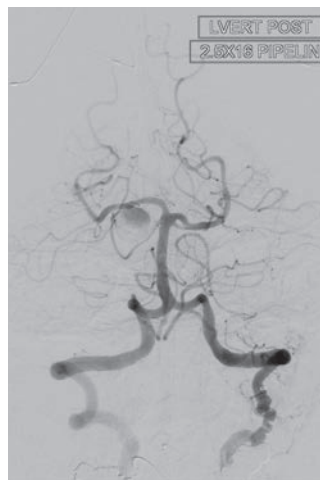
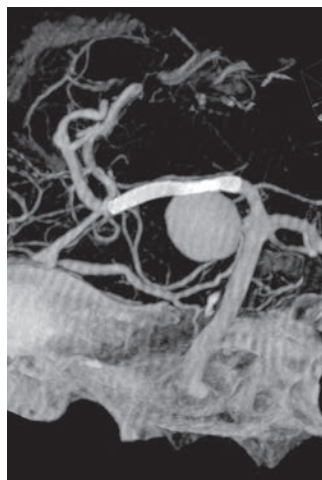
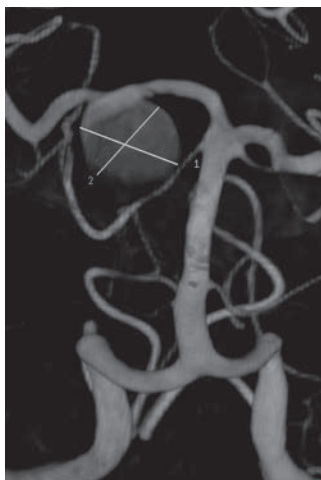




**Figure 1.**  
Head CT scan without contrast showing a hyperdense mass in the prepontine cisternae.



**Figure 2.**  
A, preprocedure CT scan showing microangiopathic changes. In addition age related widening of sulci and enlargement of ventricles can be appreciated. B, Post procedure CT scan shows PED in place. The ventricles are dilate

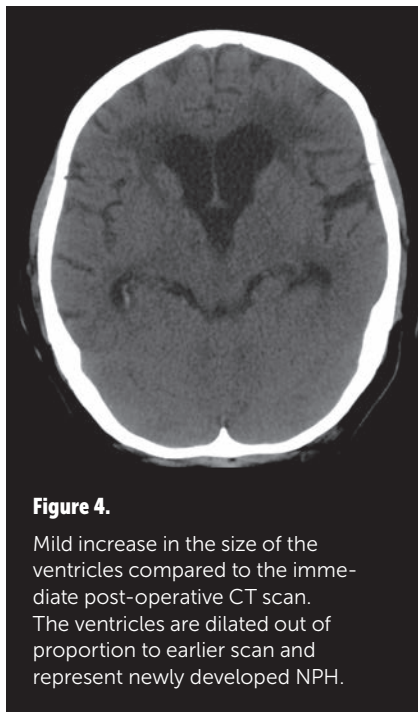


**Figure 3a-d, shown left to right, respectively.**  
a) Pre-procedural DSA shows an 11 x 12 mm P1/P2 aneurysm on the right side with a wide neck. b) DSA shows successful placement of PED (measuring 2.5 x 16 mm). c) Shows a DSA performed the following day after treatment that showed a 50% thrombosis of the aneurysm with normal flow in the parent vessel. d) 3-month follow-up angiography shows a 100% occlusion of the aneurysm.

and 0-5.5% respectively, which compares favorably to the risks associated with stent and balloon assisted coiling for unruptured aneurysms.<sup>7,11,12</sup> The major complications reported have included intracranial hemorrhage, thromboembolic events (TEE), perforator occlusion, in-stent thrombosis, mechanical delivery problems and aneurysm rupture.<sup>2,4-7,13,14</sup> However, PED is now widely used in other

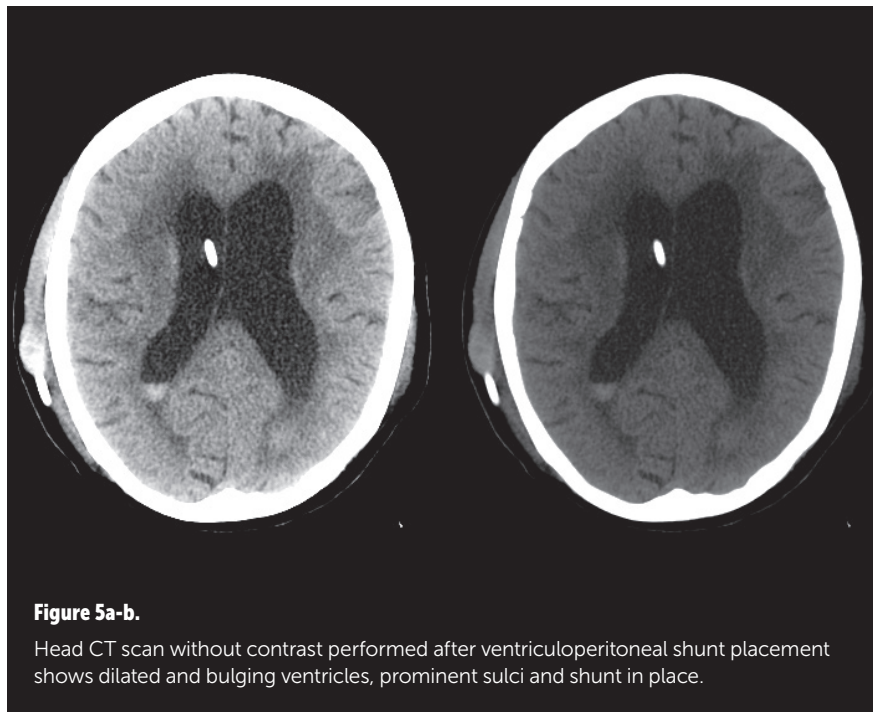
patients who do not strictly match the criteria of PUFs study.<sup>5,7,8</sup> Recent reports have mentioned unique and unusual complications, such as embolic retinal venous occlusion and shortening/migration of the PED itself.<sup>8,9</sup> To the best of our knowledge, this report is the first to describe NPH development after pipeline embolization. The diagnosis and management of NPH with a ventriculoperitoneal

shunt is well established and known to the neurosurgical community. However, managing NPH can be challenging in the acute and sub-acute setting following PED placement. The neurosurgeon must balance the risk of surgery on antiplatelet therapy with the risk of thromboembolic events, if antiplatelet therapy is to be stopped prematurely.



**Figure 4.**

Mild increase in the size of the ventricles compared to the immediate post-operative CT scan. The ventricles are dilated out of proportion to earlier scan and represent newly developed NPH.



**Figure 5a-b.**

Head CT scan without contrast performed after ventriculoperitoneal shunt placement shows dilated and bulging ventricles, prominent sulci and shunt in place.

Thromboembolic events have been estimated to complicate 8% of neuroendovascular procedures due to the thrombogenic nature of implants and guidewires.<sup>15</sup> DAPT consisting of aspirin and clopidogrel is widely used to prevent such complications.<sup>15</sup> The use of DAPT for neuroendovascular procedures has carried on from the best practice models of percutaneous coronary intervention (PCI) in interventional cardiology, where large case series have shown DAPT to be superior to aspirin alone or a combination of aspirin and warfarin in preventing thromboembolic complications.<sup>16,17</sup> At present there is no evidence from clinical trials to specifically delineate the duration of DAPT after neuroendovascular procedures and the issue remains controversial even in cardiology.<sup>18</sup>

Finally, The relationship between flow-diversion and NPH has not been described in the literature. It is already established that PED placement incites hemodynamic flow alteration and thromboemboli formation.<sup>19</sup> It is also theorized that NPH symptoms are explained by ischemic and mechanical factors.<sup>20-22</sup> Whether the appearance of NPH symptoms after PED was a simple coincidence or whether PED hastened the process remains unknown.

NPH has been previously described after the use of Hydrocoils.<sup>23</sup> The authors postulated that this complication might be due to the leakage of the hydrogel into the subarachnoid space inducing aseptic meningitis and alternating the CSF circulation. A multicenter registry that retrospectively examined the development of hydrocephalus after coiling, found that large aneurysm had a higher chance of hydrocephalus development.<sup>24</sup> The authors also reported that overt hydrocephalus developed early after coiling, while NPH tends to develop late (> 6 months). This delay makes the physiopathology less related to the physical packing of the aneurysms and more related to the inflammation and thrombosis, which might potentially release a cascade of cytokines into the subarachnoid space interfering with CSF absorption.<sup>24</sup> Large aneurysms are more likely to have a significantly larger inflammation. The HELPS trial also showed that the type of coil did not significantly affect the development of hydrocephalus post-embolization.<sup>25,26</sup> It would be interesting to start studying CSF inflammation markers after pipeline embolization to try to determine the pathophysiology or possible relationship between the pipeline device and NPH.

## CONCLUSION

Normal pressure hydrocephalus might develop as a rare complication of PED placement. The pathophysiology is still unknown. Further CSF studies would be interesting to try to establish the potential causality. Such patients can be safely and effectively treated by a ventriculoperitoneal shunt. However, the timing of surgery remains a challenge and should be delayed if possible until it is felt relatively safe to stop Plavix.

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## REFERENCES

1. D'Urso PI, Lanzino G, Cloft HJ, Kallmes DF. Flow diversion for intracranial aneurysms: a review. *Stroke* 2011; 42: 2363-8.
2. Heller RS, Dandamudi V, Lanfranchi M, Malek AM. Effect of antiplatelet therapy on thromboembolism after flow diversion with the Pipeline Embolization Device. *J Neurosurgery* 2013;119(6):1603-10
3. Nelson PK, Lylyk P, Szikora I et al. The pipeline embolization device for the intracranial treatment of aneurysms trial. *AJNR American journal of neuroradiology* 2011; 32: 34-40.
4. Szikora I, Berentei Z, Kulcsar Z et al. Treatment of intracranial aneurysms by functional reconstruction of the parent artery: the Budapest experience with the pipeline embolization device. *AJNR Am J Neuroradiol* 2010; 31: 1139-47.
5. Leung GK, Tsang AC, Lui WM. Pipeline embolization device for intracranial aneurysm: a systematic review. *Clin Neuroradiol* 2012; 22: 295-303.
6. Yavuz K, Geyik S, Saatci I, Cekirge HS. Endovascular Treatment of Middle Cerebral Artery Aneurysms with Flow Modification with the Use of the Pipeline Embolization Device. *AJNR Am J Neuroradiol* 2013 [Epub ahead of print, September 26, 2013. doi: 10.3174/ajnr.A3692]
7. Tse MM, Yan B, Dowling RJ, Mitchell PJ. Current Status of Pipeline Embolization Device in the Treatment of Intracranial Aneurysms: A Review. *World Neurosurg* 2012;80(6):829-35
8. Chalouhi N, Tjoumakaris SI, Gonzalez LF et al. Spontaneous Delayed Migration/Shortening of the Pipeline Embolization Device: Report of 5 Cases. *AJNR Am J Neuroradiol* 2013;34(12)2326-30
9. Sise AB, Osher JM, Kolsky MP et al. Pipeline Embolization Device: A New Source for Embolic Retinal Vascular Occlusion. *J Neuroophthalmol* 2013; 33(4):373-6
10. Chitale R, Gonzalez LF, Randazzo C et al. Single center experience with pipeline stent: feasibility, technique, and complications. *Neurosurgery* 2012; 71: 679-91; discussion 91.
11. Chalouhi N, Tjoumakaris S, Starke RM et al. Comparison of flow diversion and coiling in large unruptured intracranial saccular aneurysms. *Stroke; a journal of cerebral circulation* 2013; 44: 2150-4.
12. Chalouhi N, Jabbour P, Tjoumakaris S et al. Treatment of Large and Giant Intracranial Aneurysms: Cost Comparison of Flow Diversion and Traditional Embolization Strategies. *World Neurosurg* 2013; pii: S1878-8750(13)00399-9
13. Withers K, Carolan-Rees G, Dale M. Pipeline embolization device for the treatment of complex intracranial aneurysms: a NICE Medical Technology Guidance. *Appl Health Econ Health Policy* 2013; 11: 5-13.
14. Lin LM, Colby GP, Kim JE et al. Immediate and follow-up results for 44 consecutive cases of small (<10 mm) internal carotid artery aneurysms treated with the pipeline embolization device. *Surg Neurol Int* 2013; 4: 114.
15. Akbari SH, Reynolds MR, Kadkhodayan Y et al. Hemorrhagic complications after prasugrel (Effient) therapy for vascular neurointerventional procedures. *J Neurointerv Surg* 2013; 5: 337-43.
16. Schomig A, Neumann FJ, Kastrati A et al. A randomized comparison of antiplatelet and anticoagulant therapy after the placement of coronary-artery stents. *N Eng J Med* 1996; 334: 1084-9.
17. Leon MB, Baim DS, Popma JJ et al. A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting. Stent Anticoagulation Restenosis Study Investigators. *N Eng J Med* 1998; 339:1665-71.
18. Fiorella D. Anti-thrombotic medications for the neurointerventionist: aspirin and clopidogrel. *J Neurointerv Surg* 2010; 2: 44-9.
19. Fargen KM, Velat GJ, Lawson MF et al. Review of reported complications associated with the Pipeline Embolization Device. *World Neurosurg* 2012; 77(3-4): 403-4.
20. Hakim S, Vengas JG, Burton JD. The physics of the cranial cavity, hydrocephalus and normal pressure hydrocephalus: mechanical interpretation and mathematical model. *T Surg Neurol* 1970; 5: 187.
21. Koto A, Rosenberg G, Zingesser LH et al. Syndrome of normal pressure hydrocephalus: possible relation to hypertensive and arteriosclerotic vasculopathy. *J Neurol Neurosurg Psychiatry* 1977; 40: 73-9.
22. Bradley WG, Whittemore AR, Watanabe AS et al. Association of deep white matter infarction with chronic communicating hydrocephalus: implications regarding the possible origin of normal pressure hydrocephalus. *AJNR Am J Neuroradiol* 1991; 12: 31-9.
23. Deshaies EM, Adamo MA, Boulos AS. A prospective single-center analysis of the safety and efficacy of the hydrocoil embolization system for the treatment of intracranial aneurysms. *J Neurosurg* 2007; 106(2): 226-33.
24. Turner RD, da Costa LB, terBrugge KG. A multicenter registry of hydrocephalus following coil embolization of unruptured aneurysms: which patients are at risk and why it occurs. *J Neurointerv Surg* 2013; 5: 207-11.
25. White PM, Lewis SC, Gholkar A et al. Hydrogel-coated coils versus bare platinum coils for the endovascular treatment of intracranial aneurysms (HELPS): a randomised controlled trial. *Lancet* 2011; 377(9778): 1655-62.
26. White PM, Lewis SC, Nahser H et al. HydroCoil Endovascular Aneurysm Occlusion and Packing Study (HELPS trial): procedural safety and operator-assessed efficacy results. *AJNR Am J Neuroradiol* 2008; 29(2): 217-23.



# Moyamoya: A Review of the Disease and Current Treatments

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## INTRODUCTION

Moyamoya disease is a rare progressive cerebrovascular disease characterized by bilateral stenosis of vasculature of the Circle of Willis, specifically the distal internal carotid arteries, that leads to extensive collateral circulation. These dilated collateral vessels are described as having a hazy “puff of smoke” appearance on angiography. “Moyamoya” is the Japanese word for this characteristic appearance. The disease was originally described in Japan in 1957<sup>1</sup> and introduced to the English literature in 1969.<sup>2</sup> The disease is most known for its distribution in Asian populations, but recently there has been more research and attention given to moyamoya in Europe and North America. Moyamoya disease presents clinically due to the ischemic and hemorrhagic complications of abnormal cerebral vascularity.<sup>3,4</sup>

## Epidemiology

Moyamoya disease was originally described in Japanese populations but is present in a variety of ethnicities.<sup>3,5,6</sup> In Japan, the incidence per 100,000 patient years is between 0.35 to 0.943 with a male: female ratio of 1:1.87. In the US, incidence ranged from 0.05 to 0.17 per 100,000 patient years with a similar gender distribution.<sup>3,6</sup> Other population studies have not been as robust but European studies show moyamoya statistics that are more similar to American findings than those of Asian moyamoya findings.<sup>4</sup> There is a bimodal distribution of incidence: in early childhood and adulthood, but the double-peaked incidence is less dramatic in the US and Europe.<sup>4,8</sup> Children typically present with the ischemic symptoms and adults can present with either ischemic or hemorrhagic type, with the ischemic type predominating.<sup>5,9</sup> Overall, the hemorrhagic type is more common in Asia than the U.S.<sup>9</sup> The incidence has been increasing with time, which may be due to increased awareness.<sup>5</sup>

## Etiology

The etiology of moyamoya disease is largely unknown. However, there are genetic susceptibilities and biochemical correlates that warrant further research. This importance is highlighted in the 10–15% of moyamoya disease cases that are familial.<sup>10</sup> The proposed mechanism of inheritance is autosomal dominant with incomplete penetrance but it is likely there are polygenic interactions as well.<sup>11</sup> Currently, screening is not recommended for moyamoya disease.

The first gene associated with moyamoya disease was RNF213 on chromosome 17.<sup>12</sup> Animal models show that knockout of this gene causes arterial abnormalities with wall malformation and abnormal angiogenesis.<sup>13</sup> Another study showed that different mutations of this ring finger protein are associated with different clinical presentations of moyamoya: R4810K mutation with the ischemic form and A4399T mutation with the hemorrhagic form.<sup>14</sup>

There is evidence of a dysregulation of a variety of extracellular matrix proteins in moyamoya, including basic fibroblast growth factor,<sup>15</sup> transforming growth factor beta-116, and vascular endothelial growth factor.<sup>17</sup> A tentative pathologic process is believed

to be mediated by intimal thickening and media attenuation in proximal vessels, along with abnormal smooth muscle cell turnover and neovascularization in distal vessels.<sup>18</sup>

## Moyamoya Syndrome

Moyamoya disease is characterized by an idiopathic abnormal vasculature adjacent to the circle of Willis with extensive compensatory collateral vessels. Moyamoya syndrome is a separate entity, associated with another disease that causes a similar angiographic appearance.<sup>19</sup> The most common examples of diseases that can cause moyamoya syndrome are sickle-cell disease, neurofibromatosis type I, cranial irradiation, and Down syndrome. Even without these risk factors, a unilateral presentation is also considered to be moyamoya syndrome since moyamoya disease is defined as a bilateral disease.<sup>20</sup> The distinction between these two entities is critical for an appropriate clinical approach.

## CLINICAL PRESENTATION

Moyamoya disease can be asymptomatic in early stages, or present with a range of symptoms associated with the abnormal vasculature including headaches, seizures, hemiparesis, and sensory impairment. The two major types of manifestations are ischemic and hemorrhagic. Ischemic symptoms are associated with insufficient perfusion and infarcts are typically small and located in the basal ganglia.<sup>21</sup> Hemorrhages can occur due to the poorly formed collateral arterial supply and result in a worse prognosis.<sup>5</sup> Roughly half of patients have a single symptomatic episode and half have multiple recurrences of ischemic events.<sup>23</sup> Recurrences in the pediatric population are associated with stress, hyperventilation, dehydration, and crying, which are important factors to recognize and explain to the patient’s family for prevention measures.<sup>19</sup>

## DIAGNOSIS AND IMAGING

It is important that Moyamoya is considered in patients with stroke-like symptoms due to its unique clinical approach. This is especially important to keep in mind with pediatric patients since 6% of pediatric strokes are due to moyamoya disease.<sup>5,9,22</sup>

Due to the symptoms at presentation, the initial imaging study of these patients is typically computed tomography (CT). CT can identify ischemic lesions from the basal ganglia (earlier stages) to the cortex (later stages) but can be normal if the lesions are small.<sup>24</sup> Commonly, the diagnosis of moyamoya disease requires multiple imaging modalities. Brain MRI is more sensitive for these smaller lesions and can also identify punctuate flow voids in the basal ganglia which is highly suggestive of moyamoya disease.<sup>19</sup>

The gold standard for diagnosis is conventional cerebral angiography. Transcranial Doppler studies can also be useful to noninvasively detect stenotic vessels via an increased flow rate and track changes in this flow over time.<sup>25</sup>

## THERAPEUTIC OPTIONS

The mainstay of treatment for patients of all age groups presenting with Moyamoya continues to be neurosurgical intervention. Surgery is the only means by which the morbidity and mortality of the disease can be dramatically reduced. There is no agreed upon medical regimen, and the only medical options available treat the complications of the disease. For example; aspirin may be given to inhibit the formation of microthromboemboli that could cause ischemia (surgical patients are given this routinely); calcium channel blockers have been reported to improve intractable headaches; and fluids are given to avoid hypoperfusion.<sup>26</sup>

The disease is inevitably progressive,<sup>27</sup> and the single most important prognostic indicator is neurologic status at the time of treatment.<sup>26</sup> Surgery is considered first line as a preventative measure against stroke and neurologic decline,<sup>27</sup> serious complications for the relatively young patient population affected by moyamoya. If there are contraindications to surgery, such as a recent stroke or infection, or if the patient has adequate collateral circulation, medical management may

be chosen over surgery.<sup>27,28</sup> Symptomatic patients treated medically show much higher rates of recurrent stroke than surgical patients.<sup>29</sup>

### Revascularization

Surgical revascularization techniques aim to increase cerebral blood flow to affected territories, and to indirectly shrink the aberrant collaterals that have formed as a result of ICA stenosis. A variety of direct, indirect and combined surgical techniques have been employed, which can decrease the frequency of ischemic and hemorrhagic events that occur and therefore improve functional outcomes.<sup>30</sup> For the purpose of discussion, direct and indirect approaches can be separated into two distinct categories. In practice, however, the combined approach more effectively promotes long-term revascularization, and has not been proven to increase complication rates over one technique alone.<sup>23,27</sup>

### Direct Bypass

Direct revascularization involves the anastomosis of the superficial temporal artery with the middle cerebral artery, distal to the stenotic region.<sup>30</sup> This allows for an immediate increase in blood flow to previously hypoperfused territories of the brain. This method has better revascularization outcomes than indirect methods alone.<sup>25</sup> One concerning complication of this method, however, if there is inadequate blood pressure control, is postoperative hyperperfusion, which can lead to seizures.<sup>27</sup> Also, this bypass is not always feasible in children as their vessels are of a smaller diameter,<sup>27</sup> so indirect methods are often relied upon in the pediatric population.<sup>31</sup>

### Indirect Revascularization

Indirect revascularization describes a number of surgeries with the unifying theme of applying richly vascular tissue on top of the hypoperfused region in order to promote angiogenesis.<sup>27</sup> Ultimately, the transposed vessel anastomoses with the existing vasculature, which can significantly improve flow through the previously undersupplied vessels. Potential issues with this technique include the time delay of weeks to months after surgery before the target tissue is perfused, and the potential for mass effect,

as you are introducing relatively large sections of tissue into critically eloquent areas of cerebral cortex.<sup>32</sup> Tissue can be taken from, for example, the omentum (omental transplantation) or the temporalis muscle (encephalomyosynangiosis), but the three most commonly utilized indirect techniques in North America are encephaloduroarteriosynangiosis (EDAS), encephaloduroarteriomyosynangiosis (EDAMS), and multiple burr hole placement (MBH).<sup>30</sup>

The EDAS procedure requires suturing the STA and a tissue cuff to the dura overlying the target area. Burr holes are used to facilitate the craniotomy. Many variations exist, but one popular technique, pial synangiosis, involves attaching the STA and tissue cuff directly to the pia. EDAMS is a more involved procedure that involves utilization of the deep temporal, superficial temporal, and middle meningeal arteries.<sup>32</sup> MBH is the least invasive technique, more commonly used in children than adults, and requires the placement of a number of burr holes through small cuts in the periosteum. This allows for targeting of specific tissue regions and promotes angiogenesis in those areas.<sup>32</sup>

## PROGNOSIS

Moyamoya, as mentioned above, is inherently progressive.<sup>25,26</sup> The natural history of the disease cannot be changed by intervention, but it can be delayed significantly, and the functional status of the patient kept remarkably intact.<sup>30</sup> Outcomes are best predicted by neurologic status at treatment, and presentation with a stroke (hemorrhagic more than ischemic) was found to be the greatest predictor of mortality during hospital stay for treatment.<sup>5,26,27</sup> In North America, where presentation is primarily ischemic regardless of age group, childhood diagnosis is considered to have a worse prognosis.<sup>30</sup> When left untreated, even asymptomatic patients will progress to the point of potentially devastating recurrent strokes, but with early diagnosis and surgical intervention individuals can live for many years with a dramatically lower risk of the morbidities associated with moyamoya disease.<sup>33,34</sup>

## CONCLUSION

Moyamoya is a predominantly Asian cerebrovascular disease of poorly understood etiology that has seen a global increase in incidence in recent decades. Moyamoya presents on angiography with bilaterally stenosed distal ICAs and hazy dilated collateral networks; this finding can be idiopathic or present with associated diseases such as sickle cell. Initial imaging is done using CT or MRI. When symptomatic, presentation of ischemic or hemorrhagic stroke is the most common. The disease is most common in young children or middle-aged adults, with a female predominance. A variety of genetic mutations have been found to associate with the disease, but none have proven to be causative; there is likely interplay between numerous genetic and environmental factors.

The disease is inevitably progressive and cannot be reversed, but prompt intervention can dramatically reduce the likelihood of stroke and neurologic decline. Treatment methods are primarily surgical, with a combined method of direct and indirect revascularization showing the best results. STA-MCA bypass carries a risk of post-operative hyperperfusion, and is not feasible in all individuals, such as in children with small diameter vessels. Indirect revascularization requires months to form the necessary anastomoses, and carries a risk of mass effect from the introduced tissue. While moyamoya is a rare disease in the US, the ability to recognize and treat affected individuals is essential, as devastating stroke can occur if it is allowed to progress.

## REFERENCES

- Oshima H, Katayama Y: Discovery of cerebrovascular moyamoya disease: Research during the late 1950s and early 1960s. *Childs Nerv Syst* 28:497-500, 2012
- Suzuki J, Takaku A: Cerebrovascular "moyamoya" disease. disease showing abnormal net-like vessels in base of brain. *Arch Neurol* 20:288-299, 1969
- Kleinloog R, Regli L, Rinkel GJ, Klijn CJ: Regional differences in incidence and patient characteristics of moyamoya disease: A systematic review. *J Neurol Neurosurg Psychiatry* 83:531-536, 2012
- Kraemer M, Heienbrok W, Berlitz P: Moyamoya disease in europeans. *Stroke* 39:3193-3200, 2008
- Starke RM, Crowley RW, Maltenfort M, Jabbour PM, Gonzalez LF, Tjoumakaris SI, et al: Moyamoya disorder in the united states. *Neurosurgery* 71:93-99, 2012
- Uchino K, Johnston SC, Becker KJ, Tirschwell DL: Moyamoya disease in washington state and california. *Neurology* 65:956-958, 2005
- Wakai K, Tamakoshi A, Ikezaki K, Fukui M, Kawamura T, Aoki R, et al: Epidemiological features of moyamoya disease in japan: Findings from a nationwide survey. *Clin Neurol Neurosurg* 99 Suppl 2:S1-5, 1997
- Baba T, Houkin K, Kuroda S: Novel epidemiological features of moyamoya disease. *J Neurol Neurosurg Psychiatry* 79: 900-904, 2008
- Han DH, Nam DH, Oh CW: Moyamoya disease in adults: Characteristics of clinical presentation and outcome after encephaloduro-arterio-synangiosis. *Clin Neurol Neurosurg* 99 Suppl 2:S151-5, 1997
- Hoshino H, Izawa Y, Suzuki N, Research Committee on Moyamoya Disease: Epidemiological features of moyamoya disease in japan. *Neurol Med Chir (Tokyo)* 52:295-298, 2012
- Mineharu Y, Takenaka K, Yamakawa H, Inoue K, Ikeda H, Kikuta KI, et al: Inheritance pattern of familial moyamoya disease: Autosomal dominant mode and genomic imprinting. *J Neurol Neurosurg Psychiatry* 77:1025-1029, 2006
- Kamada F, Aoki Y, Narisawa A, Abe Y, Komatsuzaki S, Kikuchi A, et al: A genome-wide association study identifies RNF213 as the first moyamoya disease gene. *J Hum Genet* 56:34-40, 2011
- Liu W, Morito D, Takashima S, Mineharu Y, Kobayashi H, Hitomi T, et al: Identification of RNF213 as a susceptibility gene for moyamoya disease and its possible role in vascular development. *PLoS One* 6:e22542, 2011
- Wu Z, Jiang H, Zhang L, Xu X, Zhang X, Kang Z, et al: Molecular analysis of RNF213 gene for moyamoya disease in the chinese han population. *PLoS One* 7:e48179, 2012
- Malek AM, Connors S, Robertson RL, Folkman J, Scott RM: Elevation of cerebrospinal fluid levels of basic fibroblast growth factor in moyamoya and central nervous system disorders. *Pediatr Neurosurg* 27:182-189, 1997
- Liu C, Roder C, Schulte C, Kasuya H, Akagawa H, Nishizawa T, et al: Analysis of TGFB1 in european and japanese moyamoya disease patients. *Eur J Med Genet* 55:531-534, 2012
- Sakamoto S, Kiura Y, Yamasaki F, Shibukawa M, Ohba S, Shrestha P, et al: Expression of vascular endothelial growth factor in dura mater of patients with moyamoya disease. *Neurosurg Rev* 31:77-81; discussion 81, 2008
- Weinberg DG, Arnaout OM, Rahme RJ, Aoun SG, Batjer HH, Bendok BR: Moyamoya disease: A review of histopathology, biochemistry, and genetics. *Neurosurg Focus* 30:E20, 2011
- Roach ES, Golomb MR, Adams R, Biller J, Daniels S, Deveber G, et al: Management of stroke in infants and children: A scientific statement from a special writing group of the american heart association stroke council and the council on cardiovascular disease in the young. *Stroke* 39:2644-2691, 2008
- Research Committee on the Pathology and Treatment of Spontaneous Occlusion of the Circle of Willis, Health Labour Sciences Research Grant for Research on Measures for Intractable Diseases: Guidelines for diagnosis and treatment of moyamoya disease (spontaneous occlusion of the circle of willis). *Neurol Med Chir (Tokyo)* 52:245-266, 2012
- Morgenlander JC, Goldstein LB: Recurrent transient ischemic attacks and stroke in association with an internal carotid artery web. *Stroke* 22:94-98, 1991
- Hallemeier CL, Rich KM, Grubb RL, Jr, Chicoine MR, Moran CJ, Cross DT, 3rd, et al: Clinical features and outcome in north american adults with moyamoya phenomenon. *Stroke* 37:1490-1496, 2006
- Choi JU, Kim DS, Kim EY, Lee KC: Natural history of moyamoya disease: Comparison of activity of daily living in surgery and non surgery groups. *Clin Neurol Neurosurg* 99 Suppl 2:S11-8, 1997
- Kim JM, Lee SH, Roh JK: Changing ischaemic lesion patterns in adult moyamoya disease. *J Neurol Neurosurg Psychiatry* 80:36-40, 2009
- Lee YS, Jung KH, Roh JK: Diagnosis of moyamoya disease with transcranial doppler sonography: Correlation study with magnetic resonance angiography. *J Neuroimaging* 14:319-323, 2004
- Scott RM, Smith ER: Moyamoya disease and moyamoya syndrome. *N Engl J Med* 360:1226-1237, 2009
- Smith ER, Scott RM: Moyamoya: Epidemiology, presentation, and diagnosis. *Neurosurg Clin N Am* 21:543-551, 2010
- Kronenburg A, Braun KP, van der Zwan A, Klijn CJ: Recent advances in moyamoya disease: Pathophysiology and treatment. *Curr Neurol Neurosci Rep* 14:423-013-0423-7, 2014



29. Zhao H, You C: Comparison of one-stage direct revascularization and medicine therapy for treatment of ischemic moyamoya disease. *Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi* 23:1097-1100, 2009
30. Arias EJ, Derdeyn CP, Dacey RG, Jr, Zipfel GJ: Advances and surgical considerations in the treatment of moyamoya disease. *Neurosurgery* 74 Suppl 1:S116-25, 2014
31. Ahn IM, Park DH, Hann HJ, Kim KH, Kim HJ, Ahn HS: Incidence, prevalence, and survival of moyamoya disease in Korea: A nationwide, population-based study. *Stroke* 45:1090-1095, 2014
32. Patel NN, Mangano FT, Klimo P, Jr: Indirect revascularization techniques for treating moyamoya disease. *Neurosurg Clin N Am* 21:553-563, 2010
33. Mukawa M, Nariai T, Matsushima Y, Ohno K: Clinical features of familial juvenile cases of moyamoya disease: Analysis of patients treated in a single institute over a 28-year period. *J Neurosurg Pediatr* 12:175-180, 2013
34. Mukawa M, Nariai T, Matsushima Y, Tanaka Y, Inaji M, Maehara T, et al: Long-term follow-up of surgically treated juvenile patients with moyamoya disease. *J Neurosurg Pediatr* 10:451-456, 2012

# Cryptococcal Ventriculoperitoneal Shunt Infection: Case Report and Review of the Literature

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## INTRODUCTION

Shunting of cerebrospinal fluid using a ventriculoperitoneal (VP) shunt is the standard treatment for management of hydrocephalus.<sup>1</sup> While VP shunting is effective at reducing the morbidity and mortality associated with hydrocephalus, the high rates of complication leads to about 32% of adult patients to need revision surgery.<sup>2</sup> One of the most common complications associated with VP shunts is infection, occurring in 5.8% of patients.<sup>3,4</sup> Bacterial infection is the most commonly reported microorganism implicated in VP shunt infection.<sup>3,5,6</sup>

Fungal organisms very rarely cause VP associated infections. Only 58 cases of shunt-related fungal infections have been reported in the literature. Of these cases, the most commonly reported fungal organisms include members of the *Candida* species, as well as *Cryptococcus neoformans* and *Histoplasma capsulatum*.<sup>7</sup> In this case report we present a patient with a previously placed VP shunt, originally placed more than 20 years ago for the treatment of normal pressure hydrocephalus, who presented with confusion and difficulty ambulating. Analysis of the patient's cerebrospinal fluid from a shunt tap revealed the presence of *Cryptococcus neoformans*.

## CASE PRESENTATION

The patient is a 65 year-old male who was admitted to an outside hospital due to difficulty ambulating. The patient had a ventriculoperitoneal shunt placed more than 20 years ago for treatment of normal pressure hydrocephalus. Upon presenting to the outside hospital, he was noted to have dilated ventricles and had a large volume tap done. He was subsequently transferred to Thomas Jefferson University Hospital for further treatment. The patient was alert and oriented on admission but had lower extremity weakness (2/5). MRI showed minimal linear enhancement in the 4th ventricle and mild ependymal enhancement in the right temporal horn which was suggestive of possible infection. A shunt tap showed that his shunt was working properly, but to our surprise cerebrospinal fluid cultures revealed the presence of encapsulated yeast *Cryptococcus neoformans*.

The patient was diagnosed with an infected right occipital ventriculoperitoneal shunt. He was treated with flucytosine and amphotericin B liposome and underwent externalization of the peritoneal catheter. To ensure complete removal of the fungus, we planned for the entire shunt to be surgically removed. The patient was taken to the operating room where the shunt was removed and a right ventriculostomy was placed until the shunt could be replaced. CSF cultures remained negative for more than a week. A new VP shunt was placed 15 days following the removal of the previous shunt. The patient was discharged 1 month after admission neurologically intact and was instructed to continue amphotericin B and flucytosine. At his 3-month follow-up, the patient had remained neurologically intact and symptom free.

## DISCUSSION

Cryptococcus infection is a rare complication associated with VP shunts. Only 9 cases

of shunt related *Cryptococcus* infection have been reported in the literature.<sup>7, 8</sup> The majority of patients with cryptococcosis not associated with VP shunts are immuno-compromised; one study found that 89% percent of patients with cryptococcosis were HIV positive and 82% of HIV negative patients with cryptococcosis had at least one underlying medical condition.<sup>9,10</sup> Interestingly, 5 out of 9 of the previous cases of shunt related cryptococcosis had no underlying medical conditions.<sup>8</sup> The patient in the present case report had multiple underlying medical conditions, but was believed to be immuno-competent at the time of presentation.

In the reported cases of cryptococcal shunt infection, the time from shunt placement to symptom onset ranged from 10 days to 14 months.<sup>8,11</sup> The current case report is exceptionally unusual, with a shunt placement to symptom onset time of more than 20 years. Of the 9 previous cases of cryptococcal shunt infection, the most commonly reported symptoms were headache (44.4%, n = 4), emesis (44.4%, n=4), and fever (33.3% n=3). Three patients were treated with amphotericin B, flucytosine, and fluconazole, 5 patients were treated with amphotericin B and flucytosine, and one patient was treated with only amphotericin B.<sup>7,8</sup> Treatment included removal of the infected shunt in 8 out of 9 of the cases. One patient was successfully treated with systemic therapy alone.<sup>12</sup> Four patients died as a result of the infection or related complications.

Several possible sources for shunt related cryptococcal infection exist including shunt placement in previously infected patients, infection acquired during the shunt placement procedure, and infection occurring after shunt placement. Six of the 9 previous cases of shunt related cryptococcal infection were concluded to have resulted from shunt placement in previously infected individuals.<sup>8,13</sup> One patient developed cryptococcal shunt infection

following shunt placement; this patient had predisposing factors including small cell cancer and subsequent treatment with neuraxis irradiation.<sup>12</sup> Analysis of the source of infection for the remaining two patients were inconclusive.<sup>11, 14</sup> Due to the greater than 20 year span between shunt placement and cryptococcal infection, our patient likely was not pre-operatively infected; nor is it likely that the infection was acquired during shunt placement. Rather, it is most likely that the cryptococcal infection was acquired during the time period following shunt placement. No predisposing factors that could have contributed to the development of cryptococcal infection and explain the delayed onset were identified.

Ventriculoperitoneal shunt fungal infection is a rare but serious complication of CSF shunting. Many patients who develop shunt fungal infections were infected prior to shunt placement. Consequently, a diagnosis of fungal meningitis should be ruled out for patients presenting with hydrocephalus prior to shunt placement. Shunt cryptococcal infection can also be acquired following shunt placement, often requiring shunt removal. The present case report demonstrates that Cryptococcal shunt infections, although extremely rare, may occur more than a decade following shunt placement. Treatment involves shunt removal, anti-fungal therapy, and shunt replacement.

## REFERENCES

1. Finney, G. R. Normal pressure hydrocephalus. *Int Rev Neurobiol*, v. 84, p. 263-81, 2009. ISSN 0074-7742. Disponivel em: < <http://www.ncbi.nlm.nih.gov/pubmed/19501723> >.
2. Reddy, G. K.; Bollam, P.; Caldito, G. Ventriculoperitoneal shunt surgery and the risk of shunt infection in patients with hydrocephalus: long-term single institution experience. *World Neurosurg*, v. 78, n. 1-2, p. 155-63, Jul 2012. ISSN 1878-8750. Disponivel em: < <http://www.ncbi.nlm.nih.gov/pubmed/22120565> >.
3. Reddy, G. K. et al. Management of adult hydrocephalus with ventriculoperitoneal shunts: long-term single-institution experience. *Neurosurgery*, v. 69, n. 4, p. 774-80; discussion 780-1, Oct 2011. ISSN 1524-4040. Disponivel em: < <http://www.ncbi.nlm.nih.gov/pubmed/21508873> >.
4. Wong, J. M. et al. Patterns in neurosurgical adverse events: cerebrospinal fluid shunt surgery. *Neurosurg Focus*, v. 33, n. 5, p. E13, Nov 2012. ISSN 1092-0684. Disponivel em: < <http://www.ncbi.nlm.nih.gov/pubmed/23116093> >.
5. Rehman, A. U. et al. A simple method to reduce infection of ventriculoperitoneal shunts. *J Neurosurg Pediatr*, v. 5, n. 6, p. 569-72, Jun 2010. ISSN 1933-0715. Disponivel em: < <http://www.ncbi.nlm.nih.gov/pubmed/20515328> >.
6. Vacca, V. Diagnosis and treatment of idiopathic normal pressure hydrocephalus. *J Neurosci Nurs*, v. 39, n. 2, p. 107-11, Apr 2007. ISSN 0888-0395. Disponivel em: < <http://www.ncbi.nlm.nih.gov/pubmed/17477225> >.
7. Veeravagu, A. et al. Fungal infection of a ventriculoperitoneal shunt: histoplasmosis diagnosis and treatment. *World Neurosurg*, v. 80, n. 1-2, p. 222.e5-13, 2013 Jul-Aug 2013. ISSN 1878-8750. Disponivel em: < <http://www.ncbi.nlm.nih.gov/pubmed/23247021> >.
8. Ingram, C. W. et al. Cryptococcal ventricular-peritoneal shunt infection: clinical and epidemiological evaluation of two closely associated cases. *Infect Control Hosp Epidemiol*, v. 14, n. 12, p. 719-22, Dec 1993. ISSN 0899-823X. Disponivel em: < <http://www.ncbi.nlm.nih.gov/pubmed/8132998> >.
9. Mirza, S. A. et al. The changing epidemiology of cryptococcosis: an update from population-based active surveillance in 2 large metropolitan areas, 1992-2000. *Clin Infect Dis*, v. 36, n. 6, p. 789-94, Mar 2003. ISSN 1537-6591. Disponivel em: < <http://www.ncbi.nlm.nih.gov/pubmed/12627365> >.
10. Zarrin, M.; Zarei Mahmoudabadi, A. Central nervous system fungal infections; a review article. *Jundishapur J Microbiol*, v. 3, n. 2, p. 41-47, 2010. ISSN 2008-4161. Disponivel em: < [http://jjmicrobiol.com/?page=article&article\\_id=3830](http://jjmicrobiol.com/?page=article&article_id=3830) >.
11. TO, K. K. et al. False-negative cerebrospinal fluid cryptococcal antigen test due to small-colony variants of *Cryptococcus neoformans* meningitis in a patient with cystopleural shunt. *Scand J Infect Dis*, v. 38, n. 11-12, p. 1110-4, 2006. ISSN 0036-5548. Disponivel em: < <http://www.ncbi.nlm.nih.gov/pubmed/17148090> >.
12. Yadav, S. S.; Perfect, J.; Friedman, A. H. Successful treatment of cryptococcal ventriculoatrial shunt infection with systemic therapy alone. *Neurosurgery*, v. 23, n. 3, p. 372-3, Sep 1988. ISSN 0148-396X. Disponivel em: < <http://www.ncbi.nlm.nih.gov/pubmed/3226516> >.
13. Mangham, D. et al. Fungal meningitis manifesting as hydrocephalus. *Arch Intern Med*, v. 143, n. 4, p. 728-31, Apr 1983. ISSN 0003-9926. Disponivel em: < <http://www.ncbi.nlm.nih.gov/pubmed/6340624> >.
14. Walsh, T. J. et al. Ventriculoatrial shunt infection due to *Cryptococcus neoformans*: an ultrastructural and quantitative microbiological study. *Neurosurgery*, v. 18, n. 3, p. 373-5, Mar 1986. ISSN 0148-396X. Disponivel em: < <http://www.ncbi.nlm.nih.gov/pubmed/3517675> >.



# The ARUBA Trial: How Should We Manage Brain AVMs?

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## BACKGROUND

Brain arteriovenous malformations (bAVMs) are abnormal shunts that bypass the capillary bed and directly divert blood from the arterial to the venous circulation, without exchanging nutrients or dissipating the arterial blood pressure. They are thought to be congenital vascular lesions that occur during the late stages of fetal development, however the exact pathogenesis has not been elucidated yet.<sup>1</sup> History of hemorrhage, small AVM size, high arterial feeding blood pressure, and deep venous drainage are the main risk factors that increase the likelihood of AVM rupture. According to the American Stroke Association, 1 in 200-500 people have an AVM, while 25% of AVM patients experience seizures and 50% of patients suffer intracranial hemorrhage (ICH) at some point in their lives.<sup>2</sup> Also, 5-15% of AVM patients experience severe headaches because of the increased intracranial pressure and a similar percentage of patients exhibit neurological deficits.<sup>1</sup> With the advent of noninvasive imaging, AVMs are being detected at an early, unruptured stage, but the optimal course of action for preventing future complications still remains uncertain. The ARUBA trial strove to determine whether medical management or interventional therapy has a better long-term outcome for patients with unruptured AVMs. While it provides important data, limitations in its study design raise doubts concerning the generalizability of its findings.

The study planned to include 800 patients who were to be followed for a minimum of five and a maximum of seven years.<sup>3</sup> They were randomly assigned to one of two groups, the interventional therapy and medical management group. Patients in the medical management group received only pharmacological therapy for the medical symptoms that they experienced (unless they developed hemorrhage or infarction, in which case they were switched into the other group). Patients in the interventional therapy group received endovascular surgery, microsurgery, or radiosurgery, with or without pharmacological therapy depending on their concurrent medical conditions. The primary hypothesis was that medical management is more effective in the treatment of patients with unruptured bAVMs, the primary endpoint was death or stroke, the secondary endpoint was the quality of life, while the functional outcome status was measured using the Rankin scale.<sup>3</sup>

Previous studies had shown that early interventional treatment in patients with ruptured bAVMs is necessary and patients did not have major future clinical problems.<sup>3</sup> Interventional therapy includes endovascular surgery, which aims to occlude the nidus by delivering liquid embolics or embolic coils via a catheter, microsurgical resection of the AVM, or radiosurgery that induces a vascular injury response resulting in AVM obliteration within 1 or 2 years.<sup>1</sup> A multimodal therapy that involves more than one of these interventional procedures can also be performed on certain patients. Furthermore, medical management was shown to be very effective in treating unruptured bAVMs as indicated by the very low rate of future hemorrhage. Yet, based on data from the Columbia University Medical Center, interventional treatment of ruptured AVMs had a significantly greater likelihood of hemorrhage and/or clinical impairment (Rankin score  $\geq 2$ ) than medical

management of unruptured AVMs. It is thus imperative to compare the effectiveness of the two methods of treatment only on patients with unruptured bAVMs, since patients who present with an ICH have an already much higher risk of experiencing a subsequent ICH (hazard ratio of 3.6).<sup>4</sup> The ARUBA trial is the first study comparing medical management to surgical care on patients with unruptured bAVMs and a Rankin score less than two.<sup>3</sup>

## RESULTS

The trial started on April 4, 2007 and ended on April 15, 2013 after following 223 patients for 33 months on average. Both groups had very similar demographics, clinical symptoms, lesion characteristics and modified Rankin scores, with the exception of the interventional therapy group having a slightly higher proportion of small bAVMs (less than 3 cm).<sup>4</sup> The study ended earlier than planned because it was determined that patients who received interventional therapy had a 3-fold increase in their risk of death or stroke than those who only received pharmacological treatment.<sup>4</sup> More specifically, 10.1% of patients in the medical management group and 30.7% of patients in the interventional therapy group reached the primary endpoint, stroke or death from any cause during the study.<sup>5</sup> The primary endpoint incidence rate in the interventional therapy group was found to be very similar to the complication rates of the various invasive procedures when treating bled and unbled brain AVMs: 29% for surgery, 25% for embolization, and 13% for radiotherapy. In contrast, medical management patients had a 2.2% spontaneous rupture rate per year.<sup>4</sup>

The participants of the ARUBA trial will continue to be monitored for at least five more years in order to assess whether the differences observed in the clinical outcome and the Rankin scores will remain the same over time.

## DISCUSSION

Brain AVMs can be detected early on while they are unruptured and mostly asymptomatic, but the ideal treatment is still uncertain. The ARUBA trial argues that the best treatment for these patients is solely medical management, using anticonvulsants if the patient has seizures, and analgesics if the patient experiences headaches. However, the ARUBA trial has received plenty of criticism concerning its study design and the credibility of its findings.

The trial states that 30.7% of patients in the interventional treatment group reached the primary endpoint, but the actual symptoms experienced by the patients are not specified. The primary endpoint, stroke, is very broadly defined, including seizure, a new neurological deficit, or headache that results from ischemia or hemorrhage.<sup>7</sup> There is an obvious difference in the severity of each of these clinical presentations, but the researchers did not identify the likelihood of each symptom based on which interventional treatment the patient received.<sup>7</sup> Moreover, even though the spontaneous rupture rate per year for patients who undergo medical management is 2.2%, the rate increases with increasing age and patients continue to be at high risk throughout their lives. The complication rates of the various interventional treatments are indeed higher, however, the purpose of interventional therapy is to obliterate the bAVM so that patients can avoid increased risk and be worry-free in the future. Therefore, monitoring patients for only 33 months is inadequate; patients need to be monitored for a few decades in order to assess the risk of hemorrhage throughout their lifespan, as this is imperative information for making the right decision by both the doctor and the patient.<sup>6</sup>

Furthermore, the vast heterogeneity in the bAVM morphology and in the selection of the interventional treatment that the patients received deems

the generalizability of the trial findings questionable. First, there is concern that Mohr et al. introduced selection bias in the study by studying only relatively mild cases of bAVMs, because including only bAVMs without any previous complications is not reflective of the majority of the cases seen in the hospital. Only 13% (226 out of 1740) of the patients screened were selected, but the reasons for excluding the rest were not explicitly stated.<sup>6</sup> If the actual risk of spontaneous rupture is higher, then conservative medical management may not be sufficient. Additionally, the effectiveness of each interventional method varies drastically based on the bAVM morphology.<sup>8,9,10</sup> Mohr et al. did not provide enough information concerning the success rate of each procedure used to treat the different bAVM types. More details are needed about the embolic material used in the embolization procedures, the number and outcome of patients with total versus near-total occlusion, and the use of gamma knife versus linear accelerator in radiotherapy.<sup>7</sup> Lastly, many consider microsurgical resection of bAVMs to be more effective than embolization and radiosurgery in obliterating the nidus, yet it was used on very few patients. It was the only treatment used in 5% of the patients and used in combination with another procedure in 13% of the patients, but the reasons behind the preferential use of the other two methods over microsurgical resection were not explained.<sup>6,7</sup>

Due to these limitations in the ARUBA trial, it is questionable whether we can group all of the interventional methods together when assessing their effectiveness in curing bAVMs in comparison to medical management. More research needs to be conducted on the long-term clinical outcome of the two methods of treatment, taking into consideration the increased rupture risk with aging and the varying complication rate of the interventional methods based on the bAVM morphology.

## REFERENCES

1. Novakovic RL, Lazzaro MA, Castonguay AC, Zaidat OO. The diagnosis and management of brain arteriovenous malformations. *Neurol Clin.* 2013;31(3):749-63. doi: 10.1016/j.ncl.2013.03.003.
2. What Is an Arteriovenous Malformation (AVM)? <http://www.strokeassociation.org/>
3. STROKEORG/AboutStroke/TypesofStroke/HemorrhagicBleeds/What-Is-an-Arteriovenous-Malformation-AVM\_UCM\_310099\_Article.jsp Updated February 20, 2013. Accessed March 11, 2014.
4. Mohr JP, Parides MK, Stapf C, et al. A Randomized Multicenter Clinical Trial of Unruptured Brain AVMs (ARUBA). National Institute of Neurological Disorders and Stroke National Institutes of Health, 1 Nov. 2006. Web. 12 Mar. 2014. <http://research.ncl.ac.uk/nctu/documents/ARUBA/Protocol.pdf>
5. Halim AX, Johnston SC, Singh V, et al. Longitudinal risk of intracranial hemorrhage in patients with arteriovenous malformation of the brain within a defined population. *Stroke.* 2004;35:1697-702. <http://www.ncbi.nlm.nih.gov/pubmed/15166396>
6. Mohr JP, Parides MK, Stapf C, et al. Medical management with or without interventional therapy for unruptured brain arteriovenous malformations (ARUBA): a multicentre, non-blinded, randomised trial. *Lancet.* 2014 Feb 15; 383(9917):614-21. doi: 10.1016/S0140-6736(13)62302-8.
7. Knopman, J. and P. E. Stieg (2014). Management of unruptured brain arteriovenous malformations. *Lancet* 383(9917): 581-583.
8. Pierot, L., et al. (2014). Will A Randomized Trial of Unruptured Brain Arteriovenous Malformations Change Our Clinical Practice? *AJNR Am J Neuroradiol* 35(3): 416-417.
9. Katsaridis, V., et al. (2008). Curative embolization of cerebral arteriovenous malformations (AVMs) with Onyx in 101 patients. *Neuroradiology* 50(7): 589-597.
10. Starke, R., et al. (2013). A practical grading scale for predicting outcome after radiosurgery for arteriovenous malformations: analysis of 1012 treated patients. *J Neurosurg* 119(4): 981-987.
11. Potts, M., et al. (2013). Deep arteriovenous malformations in the Basal Ganglia, thalamus, and insula: microsurgical management, techniques, and results. *Neurosurgery* 73(3): 417-429.



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# An Update from the Division of Clinical Research



The Department of Neurosurgery at Thomas Jefferson University is a national leader in neurosurgical research. At present, the Department is conducting or participating in 26 active clinical trials and 49 retrospective studies and reviews, with additional future projects currently in the pipeline.

Our clinical trials include industry-sponsored trials as well as federally-funded, national collaborations including:

- The PROTECT Trial – for traumatic brain injury
- The BOOST Trial – for traumatic brain injury
- The SHINE Trial – for patients following stroke
- The CLEAR Trial – for patients following stroke
- The NACTN Registry – for patients following spinal cord injury
- The POINT Trial – for patients following stroke

Our Department's research spans the breadth of clinical neurosurgery, covering vascular and endovascular neurosurgery, functional neurosurgery, spine and peripheral nerve surgery, oncological neurosurgery, neuro-intensive care, and trauma. The Department's Clinical Research Unit is the only clinical research unit in the region with 24/7 staffing to conduct and support ongoing neurosurgical research projects. This unit also supports vascular neurology research stroke trials. The Department also collaborates with multiple Jefferson Hospital for Neuroscience laboratories to study behavioral and systems cognitive neuroscience, the neurobiology of disease, cellular and molecular neuroscience, and translational and clinical neuroscience. Furthermore, our state of the art telemedicine program supports our research initiatives across the region.

A listing of recently published, peer-reviewed articles authored by Jefferson neurosurgery faculty is provided below.

## **Jan Jaeger, PhD**

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## July 2013 – March 2014

- Al Khalili K, Chalouhi N, Tjomekaris S, Gonzalez LF, Starke RM, Rosenwasser R, Jabbour P. Programs Selection Criteria for Neurological Surgery Applicants in the United States: A National Survey for Neurological Surgery Program Directors. *World Neurosurg.* 2013 Aug 24. pii: S1878-8750(13)01005-X. doi:10.1016/j.wneu.2013.08.019. [Epub ahead of print] PubMed PMID: 23978450.
- Ali MS, Starke RM, Jabbour P, Tjomekaris SI, Gonzalez LF, Rosenwasser RH, Dumont AS. 184 Influxinab Suppresses TNF- $\alpha$  Induced Inflammatory Phenotype in Cerebral Vascular Smooth Muscle Cells: Implications for Cerebral Aneurysm Formation. *Neurosurgery.* 2013 Aug;60 Suppl 1:181. doi: 10.1227/01.neu.0000432774.35977.11. PubMed PMID: 23839451.
- Ali MS, Starke RM, Jabbour PM, Tjomekaris SI, Gonzalez LF, Rosenwasser RH, Owens GK, Koch WJ, Greig NH, Dumont AS. TNF- $\alpha$  induces phenotypic modulation in cerebral vascular smooth muscle cells: implications for cerebral aneurysm pathology. *J Cereb Blood Flow Metab.* 2013 Oct;33(10):1564-73. doi: 10.1038/jcbfm.2013.109. Epub 2013 Jul 17. PubMed PMID: 23860374; PubMed Central PMCID: PMC3790924.
- Andrews DW, Farrell CJ. We can control the tumor but can we stop the pain? *World Neurosurg.* 2013 Sep-Oct;80(3-4):290-2. doi: 10.1016/j.wneu.2012.05.003. Epub 2012 May 24. PubMed PMID: 22634457.
- Babiker MH, Chong B, Gonzalez LF, Cheema S, Frakes DH. Finite element modeling of embolic coil deployment: multifactor characterization of treatment effects on cerebral aneurysm hemodynamics. *J Biomech.* 2013 Nov 15;46(16):2809-16. doi: 10.1016/j.jbiomech.2013.08.021. Epub 2013 Sep 18. PubMed PMID: 24119679.
- Bhalodia V, Sestokas AK, Glassman D, Loftus W, Levin S, Contratti J, Vogel RW, Sharan AD. 172 Use of Intraoperative Collision Testing vs Electromyography for Predicting Postoperative Foot Paresthesias During Spinal Cord Stimulation. *Neurosurgery.* 2013 Aug;60 Suppl 1:177. doi: 10.1227/01.neu.0000432763.74987.65. PubMed PMID: 23839439.
- Borner C, Andrews DW. The apoptotic pore on mitochondria: are we breaking through or still stuck? *Cell Death Differ.* 2014 Feb;21(2):187-91. doi: 10.1038/cdd.2013.169. PubMed PMID: 24413197; PubMed Central PMCID: PMC3890960.
- Brennan CW, Verhaak RG, McKenna A, Campos B, Noushmehr H, Salama SR, Zheng S, Chakravarty D, Sanborn JZ, Berman SH, Beroukheim R, Bernard B, Wu CJ, Genovese G, Shmulevich I, Barnholtz-Sloan J, Zou L, Vegesna R, Shukla SA, Ciriello G, Yung WK, Zhang W, Sougnez C, Mikkelsen T, Aldape K, Bigner DD, Van Meir EG, Prados M, Sloan A, Black KL, Eschbacher J, Finocchiaro G, Friedman W, Andrews DW, Guha A, Iacocca M, O'Neill BP, Foltz G, Myers J, Weisenberger DJ, Penny R, Kucherlapati R, Perou CM, Hayes DN, Gibbs R, Marra M, Mills GB, Lander E, Spellman P, Wilson R, Sander C, Weinstein J, Meyerson M, Gabriel S, Laird PW, Haussler D, Getz G, Chin L; TCGA Research Network. The somatic genomic landscape of glioblastoma. *Cell.* 2013 Oct 10;155(2):462-77. doi: 10.1016/j.cell.2013.09.034. PubMed PMID: 24120142; PubMed Central PMCID: PMC3910500.
- Bulsara KR, Kuzmik GA, Hebert R, Cheung V, Matouk CC, Jabbour P, Hasan D, Pepper J. Stenting as monotherapy for uncoilable intracranial aneurysms. *Neurosurgery.* 2013 Sep;73(1 Suppl Operative):ons80-5; discussion ons85. doi:10.1227/NEU.0b013e31827fcaba. PubMed PMID: 23208063.
- Chalouhi N, Chitale A, Tjomekaris S, Gonzalez LF, Theofanis T, Jabbour P. Cerebellar hemorrhage from a delayed cervical spine hardware migration. *ClinNeurol Neurosurg.* 2013 Sep;115(9):1894-6. doi: 10.1016/j.clineuro.2013.05.003. Epub 2013 May 23. PubMed PMID: 23707142.
- Chalouhi N, Chitale R, Starke RM, Jabbour P, Tjomekaris S, Dumont AS, Rosenwasser RH, Gonzalez LF. Treatment of recurrent intracranial aneurysms with the Pipeline Embolization Device. *J Neurointerv Surg.* 2014 Jan 1;6(1):19-23. doi: 10.1136/neurintsurg-2012-010612. Epub 2013 Jan 23. PubMed PMID: 23345630.
- Chalouhi N, Dressler JA, Kunkel ES, Dalyai R, Jabbour P, Gonzalez LF, Starke RM, Dumont AS, Rosenwasser R, Tjomekaris S. Intravenous tissue plasminogen activator administration in community hospitals facilitated by telestroke service. *Neurosurgery.* 2013 Oct;73(4):667-71; discussion 671-2. doi: 10.1227/NEU.0000000000000073. PubMed PMID: 23842556.
- Chalouhi N, Ghobrial G, Tjomekaris S, Dumont AS, Gonzalez LF, Witte S, Davanzo J, Starke RM, Randazzo C, Flanders AE, Hasan D, Chitale R, Rosenwasser R, Jabbour P. CT perfusion-guided versus time-guided mechanical recanalization in acute ischemic stroke patients. *Clin Neurol Neurosurg.* 2013 Dec;115(12):2471-5. doi: 10.1016/j.clineuro.2013.09.036. Epub 2013 Oct 12. PubMed PMID: 24176650.
- Chalouhi N, Jabbour P, Andrews DW. Stereotactic radiosurgery for cavernous malformations: is it effective? *World Neurosurg.* 2013 Dec;80(6):e185-6. doi: 10.1016/j.wneu.2012.10.056. Epub 2012 Oct 27. PubMed PMID: 23111229.
- Chalouhi N, Jabbour P, Hasan D, Starke RM. Aspirin for prevention of subarachnoid hemorrhage: the stage is set for a randomized controlled trial. *Neurosurgery.* 2014 Jan;74(1):E147-8. doi: 10.1227/NEU.0000000000000164. PubMed PMID: 24030178.



- Chalouhi N, Jabbour P, Hasan D. Inflammation, Macrophages, and Targeted Imaging in Intracranial Aneurysms. *World Neurosurg.* 2013 Dec 16. pii: S1878-8750(13)01604-5. doi: 10.1016/j.wneu.2013.12.002. [Epub ahead of print] PubMed PMID: 24355516.
- Chalouhi N, Jabbour P, Knafo S, Abilahoud G. Adjacent segment degeneration at T1-T2: myth or reality? *Clin Neurol Neurosurg.* 2013 Sep;115(9):1921-3. doi: 10.1016/j.clineuro.2013.04.016. Epub 2013 May 17. PubMed PMID: 23688446.
- Chalouhi N, Jabbour P, Magnotta V, Hasan D. Molecular Imaging of Cerebrovascular Lesions. *Transl Stroke Res.* 2013 Oct 23. [Epub ahead of print] PubMed PMID: 24323714.
- Chalouhi N, Jabbour P, Magnotta V, Hasan D. The emerging role of ferumoxytol-enhanced MRI in the management of cerebrovascular lesions. *Molecules.* 2013 Aug 13;18(8):9670-83. doi: 10.3390/molecules18089670. PubMed PMID: 23945642.
- Chalouhi N, Jabbour P, Starke RM, Hasan DM. Aspirin for prophylaxis against cerebral aneurysm rupture. *World Neurosurg.* 2014 Jan;81(1):e2-3. doi: 10.1016/j.wneu.2013.10.010. Epub 2013 Oct 8. PubMed PMID: 24120928.
- Chalouhi N, Jabbour P, Starke RM, Zanaty M, Tjoumakaris S, Rosenwasser RH, Gonzalez LF. Treatment of a Basilar Trunk Perforator Aneurysm with the Pipeline Embolization Device. *Neurosurgery.* 2014 Jan 31. [Epub ahead of print] PubMed PMID: 24492662.
- Chalouhi N, Jabbour P. Treatment of aneurysmal subarachnoid hemorrhage in young patients. *Clin Neurol Neurosurg.* 2014 Feb;117:44. doi:10.1016/j.clineuro.2013.11.034. Epub 2013 Dec 11. PubMed PMID: 24438803.
- Chalouhi N, Osterholm J, Jabbour P, Dumont AS, Gonzalez LF, Harrop J, Sharan A, Rosenwasser R, Tjoumakaris S. History of the Department of Neurosurgery at Thomas Jefferson University Hospital. *Neurosurgery.* 2013 Oct;73(4):709-17; discussion 717-8. doi: 10.1227/01.neu.0000430299.02714.46. PubMed PMID: 23624410.
- Chalouhi N, Points L, Pierce GL, Ballas Z, Jabbour P, Hasan D. Localized increase of chemokines in the lumen of human cerebral aneurysms. *Stroke.* 2013 Sep;44(9):2594-7. doi: 10.1161/STROKEAHA.113.002361. Epub 2013 Jul 25. PubMed PMID: 23887838; PubMed Central PMCID: PMC3829607.
- Chalouhi N, Starke RM, Jabbour P, Tjoumakaris SI, Fernando Gonzalez L, Witte S, Rosenwasser RH, Dumont AS. Response. *J Neurosurg.* 2013 Dec;119(6):1654-5. PubMed PMID: 24427817.
- Chalouhi N, Starke RM, Koltz MT, Jabbour PM, Tjoumakaris SI, Dumont AS, Rosenwasser RH, Singhal S, Gonzalez LF. Stent-assisted coiling versus balloon remodeling of wide-neck aneurysms: comparison of angiographic outcomes. *AJNR Am J Neuroradiol.* 2013 Oct;34(10):1987-92. doi: 10.3174/ajnr.A3538. Epub 2013 May 2. PubMed PMID: 23639562.
- Chalouhi N, Starke RM, Tjoumakaris SI, Jabbour PM, Gonzalez LF, Hasan D, Rosenwasser RH, Dumont AS. Carotid and vertebral artery sacrifice with a combination of Onyx and coils: technical note and case series. *Neuroradiology.* 2013 Aug;55(8):993-8. doi: 10.1007/s00234-013-1203-4. Epub 2013 May 16. PubMed PMID: 23677283.
- Chalouhi N, Starke RM, Yang S, Bovenzi CD, Tjoumakaris S, Hasan D, Gonzalez LF, Rosenwasser R, Jabbour P. Extending the indications of flow diversion to small, unruptured, saccular aneurysms of the anterior circulation. *Stroke.* 2014 Jan;45(1):54-8. doi: 10.1161/STROKEAHA.113.003038. Epub 2013 Nov 19. PubMed PMID: 24253543.
- Chalouhi N, Starke RM, Yang S, Bovenzi CD, Tjoumakaris S, Hasan D, Gonzalez LF, Rosenwasser R, Jabbour P. Extending the indications of flow diversion to small, unruptured, saccular aneurysms of the anterior circulation. *Stroke.* 2014 Jan;45(1):54-8. doi: 10.1161/STROKEAHA.113.003038. Epub 2013 Nov 19. PubMed PMID: 24253543.
- Chalouhi N, Tjoumakaris S, Gonzalez LF, Dumont AS, Shah Q, Gordon D, Rosenwasser R, Jabbour P. Onyx embolization of a ruptured lenticulostriate artery aneurysm in a patient with moyamoya disease. *World Neurosurg.* 2013 Sep-Oct;80(3-4):436.e7-10. doi: 10.1016/j.wneu.2012.03.030. Epub 2012 Apr 3. PubMed PMID: 22484074.
- Chalouhi N, Tjoumakaris S, Gonzalez LF, Dumont AS, Starke RM, Hasan D, Wu C, Singhal S, Moukarzel LA, Rosenwasser R, Jabbour P. Coiling of Large and Giant Aneurysms: Complications and Long-Term Results of 334 Cases. *AJNR Am J Neuroradiol.* 2013 Aug 14. [Epub ahead of print] PubMed PMID: 23945229.
- Chalouhi N, Tjoumakaris S, Gonzalez LF, Hasan D, Alkhalili K, Dumont AS, Rosenwasser R, Jabbour P. Endovascular treatment of distal intracranial aneurysms with Onyx 18/34. *Clin Neurol Neurosurg.* 2013 Dec;115(12):2528-32. doi:10.1016/j.clineuro.2013.10.018. Epub 2013 Nov 1. PubMed PMID: 24239516.
- Chalouhi N, Tjoumakaris S, Starke RM, Gonzalez LF, Randazzo C, Hasan D, McMahon JF, Singhal S, Moukarzel LA, Dumont AS, Rosenwasser R, Jabbour P. Comparison of flow diversion and coiling in large unruptured intracranial saccular aneurysms. *Stroke.* 2013 Aug;44(8):2150-4. doi: 10.1161/STROKEAHA.113.001785. Epub 2013 May 30. PubMed PMID: 23723311.
- Chalouhi N, Tjoumakaris S, Starke RM, Hasan D, Sidhu N, Singhal S, Hann S, Gonzalez LF, Rosenwasser R, Jabbour P. Endovascular stroke intervention in young patients with large vessel occlusions. *Neurosurg Focus.* 2014 Jan;36(1):E6. doi: 10.3171/2013.9.FOCUS13398. PubMed PMID: 24380483.

- Chalouhi N, Tjoumakaris S, Thakkar V, Theofanis T, Hammer C, Hasan D, Starke RM, Wu C, Gonzalez LF, Rosenwasser R, Jabbour P. Endovascular management of cerebral vasospasm following aneurysm rupture: Outcomes and predictors in 116 patients. *Clin Neurol Neurosurg*. 2014 Mar;118C:26-31. doi: 10.1016/j.clineuro.2013.12.012. Epub 2014 Jan 4. PubMed PMID: 24529225.
- Chalouhi N, Tjoumakaris SI, Gonzalez LF, Hasan D, Pema PJ, Gould G, Rosenwasser RH, Jabbour PM. Spontaneous delayed migration/shortening of the pipeline embolization device: report of 5 cases. *AJNR Am J Neuroradiol*. 2013 Dec;34(12):2326-30. doi: 10.3174/ajnr.A3632. Epub 2013 Jun 27. PubMed PMID: 23811979.
- Chalouhi N, Witte S, Penn DL, Soni P, Starke RM, Jabbour P, Gonzalez LF, Dumont AS, Rosenwasser R, Tjoumakaris S. Diagnostic yield of cerebral angiography in patients with computed tomography-negative, lumbar puncture-positive subarachnoid hemorrhage. *Neurosurgery*. 2013 Aug;73(2):282-8. doi: 10.1227/01.neu.0000430291.31422.dd. PubMed PMID: 23615086.
- Champ CE, Palmer JD, Volek JS, Werner-Wasik M, Andrews DW, Evans JJ, Glass J, Kim L, Shi W. Targeting metabolism with a ketogenic diet during the treatment of glioblastoma multiforme. *J Neurooncol*. 2014 Jan 19. [Epub ahead of print] PubMed PMID: 24442482.
- Champ CE, Shen X, Shi W, Mayekar SU, Chapman K, Werner-Wasik M, Farrell CJ, Gunn V, Downes MB, Liu H, Evans JJ, Andrews DW. Reduced-dose fractionated stereotactic radiotherapy for acoustic neuromas: maintenance of tumor control with improved hearing preservation. *Neurosurgery*. 2013 Sep;73(3):489-96. doi: 10.1227/NEU.0000000000000019. PubMed PMID: 23756743.
- Cho W, Mason JR, Smith JS, Shimer AL, Wilson AS, Shaffrey CI, Shen FH, Novicoff WM, Fu KM, Heller JE, Arlet V. Failure of lumbopelvic fixation after long construct fusions in patients with adult spinal deformity: clinical and radiographic risk factors. *J Neurosurg Spine*. 2013 Aug 2. [Epub ahead of print] PubMed PMID: 23909551.
- Fargen KM, Blackburn S, Carpenter JS, Jabbour P, Mack WJ, Rai AT, Siddiqui AH, Turner RD, Mocco J. Early results of the Axiom MicroFX for Endovascular Repair of IntraCranial Aneurysm (AMERICA) study: a multicenter prospective observational registry. *J Neurointerv Surg*. 2013 Sep 11. doi: 10.1136/neurintsurg-2013-010887. [Epub ahead of print] PubMed PMID: 24026950.
- Fargen KM, Blackburn S, Deshaies EM, Carpenter JS, Jabbour P, Mack WJ, Rai AT, Siddiqui AH, Turner RD, Mocco J. Final results of the multicenter, prospective Axiom MicroFX for Endovascular Repair of IntraCranial Aneurysm Study (AMERICA). *J Neurointerv Surg*. 2014 Jan 6. doi: 10.1136/neurintsurg-2013-011049. [Epub ahead of print] PubMed PMID: 24394153.
- Farrell CJ, Herrmann M. Determination of vitamin D and its metabolites. *Best Pract Res Clin Endocrinol Metab*. 2013 Oct;27(5):675-88. doi: 10.1016/j.beem.2013.06.001. Epub 2013 Jul 8. PubMed PMID: 24094638.
- Fisher CG, Vaccaro AR, Whang PG, Patel AA, Thomas KC, Mulpuri K, Angevine PD, Prasad SK. Evidence-based recommendations for spine surgery. *Spine (Phila Pa 1976)*. 2013 Jan 1;38(1):E30-7. doi: 10.1097/BRS.0b013e318275cdd8. PubMed PMID: 23038617.
- Friaa O, Furukawa M, Shamas-Din A, Leber B, Andrews DW, Fradin C. Optimizing the acquisition and analysis of confocal images for quantitative single-mobile-particle detection. *Chemphyschem*. 2013 Aug 5;14(11):2476-90. doi: 10.1002/cphc.201201047. Epub 2013 Jul 3. PubMed PMID: 23824691.
- Friedel ME, Johnston DR, Singhal S, Al Khalili K, Farrell CJ, Evans JJ, Nyquist GG, Rosen MR. Airway management and perioperative concerns in acromegaly patients undergoing endoscopic transsphenoidal surgery for pituitary tumors. *Otolaryngol Head Neck Surg*. 2013 Dec;149(6):840-4. doi: 10.1177/0194599813507236. Epub 2013 Oct 3. PubMed PMID: 24091425.
- Friedel ME, Johnston DR, Singhal S, Al Khalili K, Farrell CJ, Evans JJ, Nyquist GG, Rosen MR. Airway management and perioperative concerns in acromegaly patients undergoing endoscopic transsphenoidal surgery for pituitary tumors. *Otolaryngol Head Neck Surg*. 2013 Dec;149(6):840-4. doi: 10.1177/0194599813507236. Epub 2013 Oct 3. PubMed PMID: 24091425.
- Ghobrial GM, Chalouhi N, Harrop J, Dalyai RT, Tjoumakaris S, Gonzalez LF, Hasan D, Rosenwasser RH, Jabbour P. Preoperative spinal tumor embolization: an institutional experience with Onyx. *Clin Neurol Neurosurg*. 2013 Dec;115(12):2457-63. doi: 10.1016/j.clineuro.2013.09.033. Epub 2013 Oct 12. PubMed PMID: 24169150.
- Ghobrial GM, Marchan E, Nair AK, Dumont AS, Tjoumakaris SI, Gonzalez LF, Rosenwasser RH, Jabbour P. Dural arteriovenous fistulas: a review of the literature and a presentation of a single institution's experience. *World Neurosurg*. 2013 Jul-Aug;80(1-2):94-102. doi: 10.1016/j.wneu.2012.01.053. Epub 2012 Jan 31. PubMed PMID: 22381858.
- Ghosh S, Dey S, Tjoumakaris S, Gonzalez F, Rosenwasser R, Pascal J, Jallo J. Association of morphologic and demographic features of intracranial aneurysms with their rupture: a retrospective analysis. *Acta Neurochir Suppl*. 2013;115:275-8. doi: 10.1007/978-3-7091-1192-5\_48. Review. PubMed PMID: 22890680.
- Gonzalez LF, Chalouhi N, Jabbour P, Teufack S, Albuquerque FC, Spetzler RF. Rapid and progressive venous thrombosis after occlusion of high-flow arteriovenous fistula. *World Neurosurg*. 2013 Dec;80(6):e359-65. doi: 10.1016/j.wneu.2012.10.043. Epub 2012 Oct 24. PubMed PMID: 23103261.

- Gonzalez LF, Jabbour P, Ratliff J, Tjounakaris S, Dumont A, Rosenwasser RH. Minding the stroke business. *World Neurosurg*. 2013 Sep-Oct;80(3-4):228-9. doi: 10.1016/j.wneu.2012.05.028. Epub 2012 May 24. PubMed PMID: 22633840.
- Grossman RG, Fehlings M, Frankowski R, Bureau KD, Chow D, Tator C, Teng Y, Toups EG, Harrop JS, Aarabi B, Shaffrey C, Johnson MM, Harkema S, Boakye M, Guest J, Wilson JR. A Prospective Multicenter Phase 1 Matched Comparison Group Trial of Safety, Pharmacokinetics, and Preliminary Efficacy of Riluzole in Patients with Traumatic Spinal Cord Injury. *J Neurotrauma*. 2013 Jul 16. [Epub ahead of print] PubMed PMID: 23859435.
- Hann S, Chalouhi N, Starke R, Gandhe A, Koltz M, Theofanis T, Jabbour P, Gonzalez LF, Rosenwasser R, Tjounakaris S. Comparison of neurologic and radiographic outcomes with Solitaire versus Merci/Penumbra systems for acute stroke intervention. *Biomed Res Int*. 2013;2013:715170. doi: 10.1155/2013/715170. Epub 2013 Dec 30. PubMed PMID: 24490169; PubMed Central PMCID: PMC3893791.
- Hasan DM, Chalouhi N, Jabbour P, Magnotta VA, Kung DK, Young WL. Imaging aspirin effect on macrophages in the wall of human cerebral aneurysms using ferumoxytol-enhanced MRI: preliminary results. *J Neuroradiol*. 2013 Jul;40(3):187-91. doi: 10.1016/j.neurad.2012.09.002. Epub 2013 Feb 18. PubMed PMID: 23428244.
- Higashida R, Alberts MJ, Alexander DN, Crocco TJ, Demaerschalk BM, Derdeyn CP, Goldstein LB, Jauch EC, Mayer SA, Meltzer NM, Peterson ED, Rosenwasser RH, Saver JL, Schwamm L, Summers D, Wechsler L, Wood JP; on behalf of the American Heart Association Advocacy Coordinating Committee. Interactions Within Stroke Systems of Care: A Policy Statement From the American Heart Association/American Stroke Association. *Stroke*. 2013 Aug 29. [Epub ahead of print] PubMed PMID: 23988638.
- Ho J, Ondos J, Ning H, Smith S, Kreisl T, Iwamoto F, Sul J, Kim L, McNeil K, Krauze A, Shankavaram U, Fine HA, Camphausen K. Chemoirradiation for glioblastoma multiforme: the national cancer institute experience. *PLoS One*. 2013 Aug 5;8(8):e70745. doi: 10.1371/journal.pone.0070745. Print 2013. PubMed PMID: 23940635; PubMed Central PMCID: PMC3733728.
- Jabbour P, Chalouhi N, Tjounakaris S, Gonzalez LF, Dumont AS, Randazzo C, Starke RM, Hasan D, Chitale R, Singhal S, Moukarzel LA, Rosenwasser R. The Pipeline Embolization Device: learning curve and predictors of complications and aneurysm obliteration. *Neurosurgery*. 2013 Jul;73(1):113-20; discussion 120. doi:10.1227/01.neu.0000429844.06955.39. PubMed PMID: 23615106.
- Jabbour P, Chalouhi N. Endovascular therapy for young patients with aneurysmal subarachnoid hemorrhage. *Clin Neurol Neurosurg*. 2013 Nov;115(11):2401. doi: 10.1016/j.clineuro.2013.08.029. Epub 2013 Sep 20. PubMed PMID: 24099691.
- Jabbour P, Chalouhi N. Simulation-based neurosurgical training for the presigmoid approach with a physical model. *Neurosurgery*. 2013 Oct;73 Suppl 1:81-4. doi: 10.1227/NEU.0000000000000090. PubMed PMID: 24051888.
- Jabbour P, Tjounakaris S, Chalouhi N, Randazzo C, Gonzalez LF, Dumont A, Rosenwasser R. Endovascular treatment of cerebral dural and pial arteriovenous fistulas. *Neuroimaging Clin N Am*. 2013 Nov;23(4):625-36. doi: 10.1016/j.nic.2013.03.010. Epub 2013 May 16. PubMed PMID: 24156854.
- Jabbour PM, Chalouhi N, Rosenwasser RH. The pipeline embolization device: what have we learned? *World Neurosurg*. 2013 Dec;80(6):798-9. doi: 10.1016/j.wneu.2013.01.048. Epub 2013 Jan 17. PubMed PMID: 23333996.
- Jacobs J, Weidemann CT, Miller JF, Solway A, Burke JF, Wei XX, Suthana N, Sperling MR, Sharan AD, Fried I, Kahana MJ. Direct recordings of grid-like neuronal activity in human spatial navigation. *Nat Neurosci*. 2013 Sep;16(9):1188-90. doi: 10.1038/nn.3466. Epub 2013 Aug 4. PubMed PMID: 23912946.
- Koltz MT, Chalouhi N, Tjounakaris S, Fernando Gonzalez L, Dumont A, Hasan D, Rosenwasser R, Jabbour P. Short-term outcome for saccular cerebral aneurysms treated with the Orbit Galaxy Detachable Coil System. *J Clin Neurosci*. 2014 Jan;21(1):148-52. doi: 10.1016/j.jocn.2013.08.004. Epub 2013 Aug 23. PubMed PMID:24211142.
- Kung DK, Chalouhi N, Jabbour PM, Starke RM, Dumont AS, Winn HR, Howard MA 3rd, Hasan DM. Cerebral blood flow dynamics and head-of-bed changes in the setting of subarachnoid hemorrhage. *Biomed Res Int*. 2013;2013:640638. doi: 10.1155/2013/640638. Epub 2013 Nov 25. PubMed PMID: 24371827; PubMed Central PMCID: PMC3859207.
- Kupetsky EA, Rincon F, Uitto J. Rate of change of carotid intima-media thickness with magnesium administration in Abcc6<sup>-/-</sup> mice. *Clin Transl Sci*. 2013 Dec;6(6):485-6. doi: 10.1111/cts.12057. Epub 2013 Apr 19. PubMed PMID: 24330694.
- Kupetsky EA, Rincon F. The prevalence of systemic diseases associated with dermatoses and stroke in the United States: a cross-sectional study. *Dermatology*. 2013;227(4):330-7. doi: 10.1159/000354912. Epub 2013 Nov 12. PubMed PMID: 24247071.



- Mahaney KB, Chalouhi N, Viljoen S, Smietana J, Kung DK, Jabbour P, Bulsara KR, Howard M, Hasan DM. Risk of hemorrhagic complication associated with ventriculoperitoneal shunt placement in aneurysmal subarachnoid hemorrhage patients on dual antiplatelet therapy. *J Neurosurg.* 2013 Oct;119(4):937-42. doi: 10.3171/2013.5.JNS122494. Epub 2013 Jun 28. PubMed PMID: 23808537.
- Montano-Velazquez BB, Garcia Vazquez FJ, Navarrete RC, Martinez MD, Gonzalez LF, Jauregui-Renaud K. Influence of exposure to tobacco cigarette smoke on the eosinophil count in the nasal mucosa of young patients with perennial allergic rhinitis. *Rhinology.* 2013 Sep;51(3):253-8. doi: 10.4193/Rhino12.190. PubMed PMID: 23943733.
- Monteith SJ, Tsimpas A, Dumont AS, Tjoumakaris S, Gonzalez LF, Rosenwasser RH, Jabbour P. Endovascular treatment of fusiform cerebral aneurysms with the Pipeline Embolization Device. *J Neurosurg.* 2014 Jan 24. [Epub ahead of print] PubMed PMID: 24460489.
- Parkes WJ, Nyquist GG, Rizzi C, Zhang S, Evans JJ, Heffelfinger RN, Rosen MR, Curry JM. Incidence and management of rhinosinusitis after complex orbitofacial reconstruction. *Laryngoscope.* 2013 Oct 1. doi: 10.1002/lary.24423. [Epub ahead of print] PubMed PMID: 24114760.
- Prosniak M, Harshyne LA, Andrews DW, Kenyon LC, Bedelbaeva K, Apanasovich TV, Heber-Katz E, Curtis MT, Cotzia P, Hooper DC. Glioma grade is associated with the accumulation and activity of cells bearing M2 monocyte markers. *Clin Cancer Res.* 2013 Jul 15;19(14):3776-86. doi: 10.1158/1078-0432.CCR-12-1940. Epub 2013 Jun 5. PubMed PMID: 23741072.
- Retarekar R, Ramachandran M, Berkowitz B, Harbaugh RE, Hasan D, Rosenwasser RH, Ogilvy CS, Raghavan ML. Stratification of a population of intracranial aneurysms using blood flow metrics. *Comput Methods Biomech Biomed Engin.* 2014 Feb 7. [Epub ahead of print] PubMed PMID: 24506436.
- Rincon F, Lee K. Ethical Considerations in Consenting Critically Ill Patients for Bedside Clinical Care and Research. *J Intensive Care Med.* 2013 Sep 9. [Epub ahead of print] PubMed PMID: 24019298.
- Rincon F, Mayer SA. The epidemiology of intracerebral hemorrhage in the United States from 1979 to 2008. *Neurocrit Care.* 2013 Aug;19(1):95-102. doi: 10.1007/s12028-012-9793-y. PubMed PMID: 23099848.
- Rincon F, Patel U, Schorr C, Lee E, Ross S, Dellinger RP, Zanotti-Cavazzoni S. Brain Injury as a Risk Factor for Fever Upon Admission to the Intensive Care Unit and Association With In-Hospital Case Fatality: A Matched Cohort Study. *J Intensive Care Med.* 2013 Oct 16. [Epub ahead of print] PubMed PMID: 24132129.
- Rincon F, Rossenwasser RH, Dumont A. The epidemiology of admissions of nontraumatic subarachnoid hemorrhage in the United States. *Neurosurgery.* 2013 Aug;73(2):217-23. doi: 10.1227/01.neu.0000430290.93304.33. PubMed PMID: 23615089.
- Rincon F. Studying outcomes that matter to patients and families: quality of life after intracerebral hemorrhage. *Am J Respir Crit Care Med.* 2013 Dec 1;188(11):1278-9. doi: 10.1164/rccm.201310-1836ED. PubMed PMID: 24289770.
- Rodriguez Merzagora A, Coffey TJ, Sperling MR, Sharan A, Litt B, Baltuch G, Jacobs J. Repeated stimuli elicit diminished high-gamma electrocorticographic responses. *Neuroimage.* 2013 Jul 16. doi:pii: S1053-8119(13)00758-1.10.1016/j.neuroimage.2013.07.006. [Epub ahead of print] PubMed PMID: 23867555.
- Roszelle BN, Babiker MH, Hafner W, Gonzalez LF, Albuquerque FC, Frakes DH. In vitro and in silico study of intracranial stent treatments for cerebral aneurysms: effects on perforating vessel flows. *J Neurointerv Surg.* 2013 Jul;5(4):354-60. doi: 10.1136/neurintsurg-2012-010322. Epub 2012 Jun 26. PubMed PMID: 22735859.
- Roszelle BN, Nair P, Gonzalez LF, Babiker MH, Ryan J, Frakes D. Comparison among different high porosity stent configurations: hemodynamic effects of treatment in a large cerebral aneurysm. *J Biomech Eng.* 2013 Dec 1. doi: 10.1115/1.4026257. [Epub ahead of print] PubMed PMID: 24337100.
- Sarosiek KA, Chi X, Bachman JA, Sims JJ, Montero J, Patel L, Flanagan A, Andrews DW, Sorger P, Letai A. BID preferentially activates BAK while BIM preferentially activates BAX, affecting chemotherapy response. *Mol Cell.* 2013 Sep 26;51(6):751-65. doi: 10.1016/j.molcel.2013.08.048. PubMed PMID: 24074954.
- Schaberg MR, Shah GB, Evans JJ, Rosen MR. Concomitant transsphenoidal approach to the anterior skull base and endoscopic sinus surgery in patients with chronic rhinosinusitis. *J Neurol Surg B Skull Base.* 2013 Aug;74(4):241-6. doi: 10.1055/s-0033-1342916. Epub 2013 Apr 3. PubMed PMID: 24436919; PubMed Central PMCID: PMC3715601.
- Shamas-Din A, Bindner S, Zhu W, Zaltsman Y, Campbell C, Gross A, Leber B, Andrews DW, Fradin C. tBid undergoes multiple conformational changes at the membrane required for Bax activation. *J Biol Chem.* 2013 Jul 26;288(30):22111-27. doi: 10.1074/jbc.M113.482109. Epub 2013 Jun 6. PubMed PMID: 23744079; PubMed Central PMCID: PMC3724664.
- Shields CL, Kaliki S, Al-Dahmash S, Rojanaporn D, Leahey A, Griffin G, Jabbour P, Shields JA. Management of advanced retinoblastoma with intravenous chemotherapy then intra-arterial chemotherapy as alternative to enucleation. *Retina.* 2013 Nov-Dec;33(10):2103-9. doi: 10.1097/IAE.0b013e318295f783. PubMed PMID: 23873161.

- Starke RM, Ali MS, Jabbour PM, Tjournakaris SI, Gonzalez F, Hasan DM, Rosenwasser RH, Owens GK, Koch WJ, Dumont AS. Cigarette smoke modulates vascular smooth muscle phenotype: implications for carotid and cerebrovascular disease. *PLoS One*. 2013 Aug 14;8(8):e71954. doi: 10.1371/journal.pone.0071954. eCollection 2013. PubMed PMID: 23967268; PubMed Central PMCID: PMC3743809.
- Starke RM, Chalouhi N, Ali MS, Jabbour P, Tjournakaris SI, Gonzalez LF, Rosenwasser RH, Owens G, Greig NH, Dumont AS. 190 Critical Role of TNF- $\alpha$  in Cerebral Aneurysm Formation and Rupture. *Neurosurgery*. 2013 Aug;60 Suppl 1:183. doi: 10.1227/01.neu.0000432780.74094.e2. PubMed PMID: 23839457.
- Starke RM, Chalouhi N, Ali MS, Jabbour PM, Tjournakaris SI, Gonzalez LF, Rosenwasser RH, Koch WJ, Dumont AS. The role of oxidative stress in cerebral aneurysm formation and rupture. *Curr Neurovasc Res*. 2013 Aug;10(3):247-55. PubMed PMID: 23713738; PubMed Central PMCID: PMC3845363.
- Starke RM, Chalouhi N, Ali MS, Penn DL, Tjournakaris SI, Jabbour PM, Gonzalez LF, Rosenwasser RH, Dumont AS. Endovascular treatment of very small ruptured intracranial aneurysms: complications, occlusion rates and prediction of outcome. *J Neurointerv Surg*. 2013 Nov;5 Suppl 3:iii66-71. doi: 10.1136/neurintsurg-2012-010537. Epub 2012 Nov 17. PubMed PMID: 23161801.
- Starke RM, Chalouhi N, Ali MS, Tjournakaris SI, Jabbour PM, Fernando Gonzalez L, Rosenwasser RH, Dumont AS. Endovascular treatment of carotid cavernous aneurysms: Complications, outcomes and comparison of interventional strategies. *J Clin Neurosci*. 2013 Aug 20. doi:pii: S0967-5868(13)00194-X. 10.1016/j.jocn.2013.03.003. [Epub ahead of print] PubMed PMID: 23972560.
- Tsimpas A, Chalouhi N, Halevy JD, Tjournakaris S, Gonzalez LF, Monteith SJ, Dumont AS, Rosenwasser R, Jabbour P. The use of adenosine in the treatment of a high-flow vein of Galen malformation in an adult. *J Clin Neurosci*. 2013 Dec 13. pii: S0967-5868(13)00653-X. doi: 10.1016/j.jocn.2013.11.014. [Epub ahead of print] PubMed PMID: 24491583.
- Urtecho J, Snapp M, Sperling M, Maltenfort M, Vibbert M, Athar MK, McBride W, Moussouttas M, Bell R, Jallo J, Rincon F. Hospital mortality in primary admissions of septic patients with status epilepticus in the United States\*. *Crit Care Med*. 2013 Aug;41(8):1853-62. doi: 10.1097/CCM.0b013e31828a3994. PubMed PMID: 23782964.
- Vaccaro AR, Fisher CG, Patel AA, Prasad SK, Chi J, Mulpuri K, Thomas KC, Whang PG. Evidence-based recommendations for spine surgery. *Spine (Phila Pa 1976)*. 2013 Jul 1;38(15):E970-8. doi: 10.1097/BRS.0b013e3182982d32. PubMed PMID: 23629483.
- van Gerven MA, Maris E, Sperling M, Sharan A, Litt B, Anderson C, Baltuch G, Jacobs J. Decoding the memorization of individual stimuli with direct human brain recordings. *Neuroimage*. 2013 Apr 15;70:223-32. doi:10.1016/j.neuroimage.2012.12.059. Epub 2013 Jan 5. PubMed PMID: 23298746; PubMed Central PMCID: PMC3580011.
- Vanner SA, Li X, Zvanych R, Torchia J, Sang J, Andrews DW, Magarvey NA. Chemical and biosynthetic evolution of the antimycin-type depsipeptides. *Mol Biosyst*. 2013 Nov;9(11):2712-9. doi: 10.1039/c3mb70219g. PubMed PMID: 23989727.
- Zanaty M, Chalouhi N, Starke RM, Tjournakaris S, Gonzalez LF, Hasan D, Rosenwasser R, Jabbour P. Endovascular treatment of cerebral mycotic aneurysm: a review of the literature and single center experience. *Biomed Res Int*. 2013;2013:151643. doi: 10.1155/2013/151643. Epub 2013 Dec 9. Review. PubMed PMID: 24383049; PubMed Central PMCID: PMC3872026.
- Zanaty M, Chalouhi N, Tjournakaris SI, Rosenwasser RH, Jabbour PM. Endovascular Management of Cerebral Aneurysm : Review of the Literature. *TranslStroke Res*. 2013 Nov 24. [Epub ahead of print] PubMed PMID: 24323730.



# JHN TEAM VASCULAR



S. Tjoumakaris, MD

R. Rosenwasser, MD

P. Jabbour, MD



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# Support Groups

## Brain Aneurysm and AVM Support Group at Jefferson

The Brain Aneurysm and AVM (arteriovenous malformation) Support Group provides support for individuals, family members and friends who have been affected by cerebral aneurysms, subarachnoid hemorrhage and AVMs. The purpose of the group is to gain and share knowledge and understanding of these vascular anomalies and the consequences of these disease processes. The group provides mutual support to its members by creating an atmosphere that engenders active listening and sincere and thoughtful speech within a caring environment.

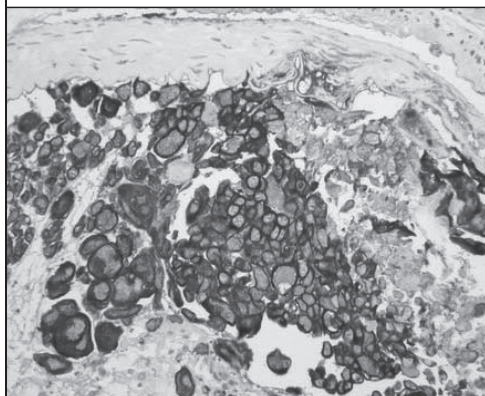
<b>When</b>	Third Wednesday of every month (September through June)
<b>Time</b>	6:30-8:30 p.m.
<b>Place</b>	909 Walnut Street, 3rd Floor, Conference Room Philadelphia, PA 19107
<b>Moderator/ Secretary</b>	Jill Galvao
<b>Parking</b>	Complimentary parking is provided in the parking garage located in the JHN Building (Jefferson Hospital for Neuroscience) on 9th Street (between Locust & Walnut)
<b>Information</b>	For additional information please call: 215-503-1714

## The Brain Tumor Support Group at Jefferson

The Delaware Valley Brain Tumor Support Group at Jefferson provides an opportunity for patients and their families to gain support in obtaining their optimum level of well-being while coping with, and adjusting to the diagnosis of brain tumor. Members are encouraged to share their support strategies so members can confront the challenges that this disease process has imposed on their lives. The strength gained from group can be a source of comfort and hope for whatever lies ahead.

<b>When</b>	Second Thursday of every month
<b>Time</b>	7-8:30 p.m.
<b>Place</b>	Jefferson Hospital for Neuroscience, 3rd Floor conference room 900 Walnut Street Philadelphia, PA 19107
<b>Facilitator</b>	Joseph McBride, BSN, RN and Katelyn Salvatore, BSN, RN. 215-955-4429

Light refreshments and snacks will be served. Free parking is available at the Jefferson Hospital for Neuroscience parking lot.



## Neurosurgical Emergency Hotline

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# UPCOMING JEFFERSON NEUROSURGERY CME PROGRAMS

As an integral part of Jefferson Hospital for Neuroscience, the region's only dedicated hospital for neuroscience, the Department of Neurological Surgery is one of the busiest academic neurosurgical programs in the country, offering state-of-the-art treatment to patients with neurological diseases affecting the brain and spine, such as brain tumors, spinal disease, vascular brain diseases, epilepsy, pain, Parkinson's disease and many other neurological disorders (<http://www.jefferson.edu/jmc/departments/neurosurgery.html>).

As part of a larger educational initiative from the Jefferson Department of Neurological Surgery, the Jefferson Office of Continuing Medical Education is offering the following continuing professional educational opportunities for 2014-2015:

- **4th Annual Brain Tumor Symposium**  
*October 31, 2014*  
*Hyatt Regency Philadelphia at Penn's Landing*
- **26th Annual Pan Philadelphia Neurosurgery Conference**  
*December 5, 2014*  
*The Union League of Philadelphia*
- **Fundamental Critical Care Support Course**  
*December 15-16, 2014*  
*Campus of Thomas Jefferson University*
- **4th Annual Neurocritical Care Symposium**  
*January/February 2015*  
*Location TBD*
- **14th Annual Cerebrovascular Update**  
*March 2015*  
*Hyatt at the Bellevue, Philadelphia*
- **6th Annual Navigating Spinal Care Symposium**  
*May 2015*  
*Location TBD*

For additional information regarding these and other Jefferson CME programs, please visit our website at <http://jeffline.jefferson.edu/jeffcme/> or call the Office of CME at 888-JEFF-CME (888-533-3263).

Jefferson Medical College of Thomas Jefferson University is accredited by the ACCME to provide continuing medical education for physicians.



# Neurosurgery Grand Rounds

## Overall Goals & Objectives

- Evaluate current controversies in neurosurgery
- Discuss routine occurrences in neurosurgical practice and evaluate them in terms of outcome and alternative methods of management
- Review recent advances and current therapeutic options in the treatment of various neurosurgical disorders.

Jefferson Medical College of Thomas Jefferson University is accredited by the ACCME to provide continuing medical education for physicians.

Jefferson Medical College designates this educational activity for a maximum of 1 AMA PRA Category 1 Credit(s)(TM). Physicians should only claim credit commensurate with the extent of their participation in the activity.

For additional information and a schedule of speakers, please contact:

Janice Longo

**215-503-7008**

[janice.longo@jefferson.edu](mailto:janice.longo@jefferson.edu)

**Fridays, 7:00 am**

De Palma Auditorium

**1025 Walnut Street  
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# SAVE THE DATE

## 26<sup>th</sup> ANNUAL PAN PHILADELPHIA NEUROSURGERY CONFERENCE DECEMBER 5, 2014

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