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

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

The ARUBA Trial: How Should We Manage Brain AVMS?
# Table of Contents

**Predictors of Seizures Following Cranioplasty**
Mario Zanaty, MD; Nohra Chalouhi, MD; Robert Rosenwasser, MD; and Pascal Jabbour, MD; Stavropoula Tjoumakaris, MD

**Concurrent Metastatic Colon Adenocarcinoma and Vertebral Osteomyelitis: A Case Report**
Kelly Krupa, BS; Kristin Krupa, BS; Thana Theofanis, MD; Ravichandra Madineni, MD; Dr. James Harrop, MD; Jack Jallo, MD, PhD; Srinivas Prasad, MD; Ashwini Sharan, MD; Joshua Heller, MD

**Hydrocephalus, a Complication of Flow-diversion?**
Mario Zanaty, MD; Muhammad Babar Khan, BS; Nohra Chalouhi, MD; Stavropoula I. Tjoumakaris, MD; Robert H. Rosenwasser, MD; Pascal Jabbour MD

**Moyamoya: A Review of the Disease and Current Treatments**
Eliza Anderson, BA; Cory Bovenzi, BA; Thana Theofanis, MD; Nohra Chalouhi, MD; Robert H. Rosenwasser, MD; Pascal Jabbour, MD; Stavropoula Tjoumakaris, MD

**Cryptococcal Ventriculoperitoneal Shunt Infection: Case Report and Review of the Literature**
Matthew Viereck, BS; Nohra Chalouhi, MD; David Krieger, MD; Kevin Judy, MD

**The ARUBA Trial: How Should We Manage Brain AVMs?**
Nikolaos Mouchtouris, BS; Nohra Chalouhi, MD; Thana Theofanis, MD; Mario Zanaty, MD; Stavropoula I. Tjoumakaris, MD; Robert Rosenwasser, MD; Pascal Jabbour, MD

**Departmental Information**
Contact Information

**Research Studies**
Recently Published Articles
Support Groups
Contact
Predictors of Seizures Following Cranioplasty

Mario Zanaty, MD1; Nohra Chalouhi, MD1; Robert Rosenwasser, MD1; and Pascal Jabbour, MD1; Stavropoula Tjoumakaris, MD1

1 Department of Neurosurgery, Thomas Jefferson University and Jefferson Hospital for Neuroscience, Philadelphia, Pennsylvania

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. 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. 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 material type (autologous vs. synthetic). A multivariate logistic regression analysis was performed.

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 \(p<0.15\) 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 reach statistical significant \((p>0.05)\) (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

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Odds Ratio, (P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>OR=2.35 (P&lt;0.05)</td>
</tr>
<tr>
<td>Increasing age</td>
<td>OR=1.04 (P&lt;0.05)</td>
</tr>
<tr>
<td>Infection</td>
<td>OR=4.12 (P&lt;0.05)</td>
</tr>
<tr>
<td>Trauma</td>
<td>OR=2.17 (P=0.07)</td>
</tr>
<tr>
<td>Bifrontal/convex</td>
<td>OR=2.86 (P=0.06)</td>
</tr>
</tbody>
</table>

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 and may independently contribute to post-operative seizure. In a recent retrospective study, cranioplasty was an independent risk factor for seizures occurrence in patients undergoing decompressive hemicraniectomy (DHC) for stroke or trauma. 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. Free radical formation, ionic balance disturbance, and cerebral manipulation have been postulated as a mechanism of post-operative seizure formation. 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, Creuztfeldt et al. found that seizures were more common in males. None of the continuous variables in their study, which included age, Glasgow coma scale and National Institute of Health Stroke Scale, was associated with...
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. When extensive damage occurs, iron accumulation in the tissue undergoes a chain of oxidoreduction reactions that generates bioactive free radicals. This is believed to lead to the formation of epileptic foci responsible for late epilepsy. Earlier studies argued that cranioplasty might decrease the risk of post-traumatic epilepsy, but when groups with similar injury were compared, no significant statistical differences were noted in the seizure rates related to the cranioplasty itself. 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 localization). 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. 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.

### 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. When extensive damage occurs, iron accumulation in the tissue undergoes a chain of oxidoreduction reactions that generates bioactive free radicals. This is believed to lead to the formation of epileptic foci responsible for late epilepsy. Earlier studies argued that cranioplasty might decrease the risk of post-traumatic epilepsy, but when groups with similar injury were compared, no significant statistical differences were noted in the seizure rates related to the cranioplasty itself. 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 localization). 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. 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. 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%. 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.
REFERENCES


Concurrent Metastatic Colon Adenocarcinoma and Vertebral Osteomyelitis: A Case Report

Kelly Krupa, BS\(^1\); Kristin Krupa, BS\(^1\); Thana Theofanis, MD\(^2\); Ravichandra Madineni, MD\(^2\); Dr. James Harrop, MD\(^2\); Jack Jallo, MD, PhD\(^2\); Srinivas Prasad, MD\(^2\); Ashwini Sharan, MD\(^2\); Joshua Heller, MD\(^2\)

\(^1\) Third Year Medical Students, Jefferson Medical College, Philadelphia, PA
\(^2\) Department of Neurological Surgery, Thomas Jefferson University Hospital, Philadelphia, PA

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.

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 temporo-occipital 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).

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 arthrodesis 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. 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. The mortality for vertebral osteomyelitis ranges from 2-20% and high rates of morbidity exist among survivors. Staphylococcus aureus, seen in 55-90% of cases, is the most common causative agent in pyogenic vertebral osteomyelitis. Complications of vertebral osteomyelitis can include direct seeding of other compartments leading to para-vertebral, epidural, or psoas abscesses. Patients with vertebral osteomyelitis commonly present initially with back pain. The infection site determines where the patient will experience pain, with the lumbar spine being the most common site (58%). Some patients will present with various neurologic deficits such as sensory loss, lower extremity weakness, paraplegia and radiculopathy. Vertebral osteomyelitis can exist as an acute (occurring over a few days or weeks) or chronic process (lasting for weeks or months). 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. 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. In about half of all cases the source of infection is found.

Laboratory findings of patients with vertebral osteomyelitis depend on the grade of the pathologic process and the causative agent. 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. 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. Magnetic resonance imaging (MRI) should be the initial choice for imaging in patients with neurologic impairment. MRI is the method of choice and has a high accuracy (90%) for diagnosing vertebral osteomyelitis. 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. 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.

Computed tomography (CT) has a lower sensitivity compared to MRI and has therefore a minor role in diagnosing early vertebral osteomyelitis. 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.

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. 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. 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. 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.

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.

The first imaging technique historically utilized to diagnose 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 anteroposterior view. Radiographs also show bone destruction and sclerosis. 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. 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.

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. 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. 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.

REFERENCES
Hydrocephalus, a Complication of Flow-diversion?

Mario Zanaty, MD; Muhammad Babar Khan, BS; Nohra Chalouhi, MD; Stavropoula I. Tjoumakaris, MD; Robert H. Rosenwasser, MD; Pascal Jabbour MD

1 Department of Neurosurgery, Thomas Jefferson University and Jefferson Hospital for Neuroscience, Philadelphia, PA.
2 Visiting Medical Student, Department of Neurosurgery, Thomas Jefferson University and Jefferson Hospital for Neuroscience, Philadelphia, PA.

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.1 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%.2-7 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.7-10 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).5,7 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%
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.

and 0-5.5% respectively, which compares favorably to the risks associated with stent and balloon assisted coiling for unruptured aneurysms. The major complications reported have included intracranial hemorrhage, thromboembolic events (TEE), perforator occlusion, in-stent thrombosis, mechanical delivery problems and aneurysm rupture. However, PED is now widely used in other patients who do not strictly match the criteria of PUFS study. Recent reports have mentioned unique and unusual complications, such as embolic retinal venous occlusion and shortening/migration of the PED itself. 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.
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.

**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.

**Conflict of interest:** the corresponding author Pascal Jabbour M.D is a consultant at Covidien

**GRANT SUPPORT**

None

**ACKNOWLEDGMENT**

none
REFERENCES


Moyamoya: A Review of the Disease and Current Treatments

Eliza Anderson, BA1; Cory Bovenzi, BA1; Thana Theofanis, MD2; Nohra Chalouhi, MD2; Robert H. Rosenwasser, MD2; Pascal Jabbour, MD2; Stavropoula Tjoumakaris, MD2

1 Third Year Medical Student, Jefferson Medical College, Philadelphia, PA
2 Department of Neurological Surgery, Thomas Jefferson University Hospital, Philadelphia, PA

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 and introduced to the English literature in 1969. 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 American. Moyamoya disease presents clinically due to the ischemic and hemorrhagic complications of abnormal cerebral vasculature.

Epidemiology

Moyamoya disease was originally described in Japanese populations but is present in a variety of ethnicities. In Japan, the incidence per 100,000 patient years is between 0.35 to 0.943 with a male:female ratio of 1.1:1.87. In the US, incidence ranged from 0.05 to 0.17 per 100,000 patient years with a similar gender distribution. 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. 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. Children typically present with the ischemic symptoms and adults can present with either ischemic or hemorrhagic type, with the ischemic type predominating. Overall, the hemorrhagic type is more common in Asia than in the U.S. The incidence has been increasing with time, which may be due to increased awareness.

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. The proposed mechanism of inheritance is autosomal dominant with incomplete penetrance. Since moyamoya disease is defined as a bilateral disease, the distinction between these two entities is critical for an appropriate clinical approach.

The first gene associated with moyamoya disease was RNF213 on chromosome 17. Animal models show that knockout of this gene causes arterial abnormalities with wall malformation and abnormal angiogenesis. 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.

There is evidence of a dysregulation of a variety of extracellular matrix proteins in moyamoya, including basic fibroblast growth factor, transforming growth factor beta-116, and vascular endothelial growth factor. 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.

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. The most common 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. 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. Hemorrhages can occur due to the poorly formed collateral arterial supply and result in a worse prognosis. Roughly half of patients have a single symptomatic episode and half have multiple recurrences of ischemic events. 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.
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.5,9,22

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.24 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.19

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.25

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 hypoprefusion.26

The disease is inevitably progressive.27 and the single most important prognostic indicator is neurologic status at the time of treatment.26 Surgery is considered first line as a preventative measure against stroke and neurologic decline.27 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.27,28 Symptomatic patients treated medically show much higher rates of recurrent stroke than surgical patients.29

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.30 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.30,27

Direct Bypass

Direct revascularization involves the anastomosis of the superficial temporal artery with the middle cerebral artery, distal to the stenotic region.30 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.23 One concerning complication of this method, however, if there is inadequate blood pressure control, is postoperative hyperperfusion, which can lead to seizures.27 Also, this bypass is not always feasible in children as their vessels are of a smaller diameter.27 so indirect methods are often relied upon in the pediatric population.31

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.27 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.32 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), encephaloduroarteriomysynangiosis (EDAMS), and multiple burr hole placement (MBH).10

The EDAS procedure requires sutting 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.32 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.32

PROGNOSIS

Moyamoya, as mentioned above, is inherently progressive.25,26 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.30 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.5,26,27 In North America, where presentation is primarily ischemic regardless of age group, childhood diagnosis is considered to have a worse prognosis.30 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.33,34
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


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

Matthew Viereck, BS1; Nohra Chalouhi, MD2; David Krieger, MD2; Kevin Judy, MD2

1 Second Year Medical Student, Jefferson Medical College, Philadelphia, PA
2 Department of Neurological Surgery, Thomas Jefferson University Hospital, Philadelphia, PA

INTRODUCTION

Shunting of cerebrospinal fluid using a ventriculoperitoneal (VP) shunt is the standard treatment for management of hydrocephalus.1 While VP shunting is effective at reducing the morbidity and mortality associated with hydrocephalus, the high rates of complication lead to about 32% of adult patients to need revision surgery.2 One of the most common complications associated with VP shunts is infection, occurring in 5.8% of patients.3,4 Bacterial infection is the most commonly reported microorganism implicated in VP shunt infection.3,5,6 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.7 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 fluconosine and amphotericin B liposome and underwent externalization of the peritoneal catheter. To ensure complete removal of the fungus, we planned 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 fluconosine. 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.7,8 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.9,10 Interestingly, 5 out of 9 of the previous cases of shunt related cryptococcal infection had no underlying medical conditions.8 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.8,11 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, fluclotyosine, and fluconazole, 5 patients were treated with amphotericin B and fluclotyosine, and one patient was treated with only amphotericin B.7,8 Treatment included removal of the infected shunt in 8 out of 9 of the cases. One patient was successfully treated with systemic therapy alone.12 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.8,13 One patient developed cryptococcal shunt infection due to...
following shunt placement; this patient had predisposing factors including small cell cancer and subsequent treatment with neuraxis irradiation. Analysis of the source of infection for the remaining two patients were inconclusive. 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


The ARUBA Trial: How Should We Manage Brain AVMs?

Nikolaos Mouchtouris, BS1; Nohra Chalouhi, MD2; Thana Theofanis, MD2; Mario Zanaty, MD2; Stavroula I. Tjoumakaris, MD2; Robert Rosenwasser, MD2; Pascal Jabbour, MD2

1 Second Year Medical Student, Jefferson Medical College, Philadelphia, PA
2 Department of Neurological Surgery, Thomas Jefferson University Hospital, Philadelphia, PA

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.1 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.2 Also, 5-15% of AVM patients experience severe headaches because of the increased intracranial pressure and a similar percentage of patients exhibit neurological deficits.1 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.3 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.3

Previous studies had shown that early interventional treatment in patients with ruptured bAVMs is necessary and patients did not have major future clinical problems.3 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.1 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 ≥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).4 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.5

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).4 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. 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.5 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.4

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. 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.

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.

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. 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. 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.

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.

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
The power of a single brain is remarkable. So imagine when we put great brains together.

Disorders of the brain and spine are complex. But finding the right doctor is simple. As the Philadelphia area’s only hospital dedicated to neuroscience, Jefferson Hospital for Neuroscience combines world-class specialists, compassionate caring, advanced treatment technologies and leading-edge research to devise aggressive treatment plans for patients with everything from aneurysms to epilepsy. And when our neurologists, neurosurgeons, radiation oncologists and radiologists put their heads together, you’re connected to the best care anywhere.

MAKE THE CONNECTION

Disorders of the brain and spine are complex. But finding the right doctor is simple. As the Philadelphia area’s only hospital dedicated to neuroscience, Jefferson Hospital for Neuroscience combines world-class specialists, compassionate caring, advanced treatment technologies and leading-edge research to devise aggressive treatment plans for patients with everything from aneurysms to epilepsy. And when our neurologists, neurosurgeons, radiation oncologists and radiologists put their heads together, you’re connected to the best care anywhere.

1-800-JEFF-NOW JeffersonHospital.org/neuroscience

James S. Harrop, MD, Neurosurgeon
Departmental Information

Thomas Jefferson University
Department of Neurological Surgery

Locations

Center City
909 Walnut Street, 2nd and 3rd Floors
Philadelphia, PA 19107
Telephone: 215-955-7000
www.Jefferson.edu/Neurosurgery

Voorhees
443 Laurel Oak Drive, 2nd Floor
Voorhees, NJ 08043

Langhorne
St. Mary Medical Center
1205 Langhorne-Newtown Road, Suite 210
Langhorne, PA 19047

Kennedy
445 Hurffville-Cross Keys Road
Washington Township, NJ 08080

Bryn Mawr Hospital
130 S. Bryn Mawr Avenue, Suite 209
Bryn Mawr, PA 19010.

Lankenau Medical Center
MOB West 430
100 Lancaster Avenue
Wynnewood, PA 19096.

Faculty

David W. Andrews, MD, FACS
Professor and Vice Chair for Clinical Services
Ethan Benardete, MD, PhD
Assistant Professor
William A Buchheit, MD, FACS
Professor Emeritus and Former Chair
Melanie B. Elliott, PhD, Med
Assistant Professor
James J. Evans, MD, FACS
Associate Professor
Christopher J. Farrell, MD
Assistant Professor
Jon Glass, MD
Associate Professor of Neurology and Neurological Surgery
Grahame Gould, MD
Instructor
Gaurav Jain, MD
Assistant Professor
James S. Harrop, MD, FACS
Professor
Larry A. Harshyne, Jr, PhD
Instructor
Joshua E. Heller, MD
Assistant Professor
Pascal M. Jabbour, MD
Associate Professor
Jack I. Jalil, MD, PhD, FACS
Professor and Vice Chair for Academic Services
Kevin D. Judy, MD, FACS
Professor
M. Kamran Athar, MD
Assistant Professor of Internal Medicine and Neurological Surgery
Lyndon J. Kim, MD
Associate Professor of Medical Oncology and Neurological Surgery

Anil Nair, MD
Instructor
Jewell L. Osterholm, MD, FACS
Professor Emeritus and Former Chair
Srinivas K. Prasad, MD
Assistant Professor
Fred Rincon, MD
Assistant Professor of Neurology and Neurological Surgery
Robert H. Rosenwasser, MD, FACS, FAHA
Professor and Chair

Ashwini D. Sharan, MD, FACS
Professor
Stavropoula I. Tjoumakaris, MD
Assistant Professor
Jacqueline Urtecho, MD
Assistant Professor of Neurology and Neurological Surgery
Matthew Vibbert, MD
Assistant Professor of Neurology and Neurological Surgery
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
jan.jaeger@jefferson.edu
Director of Clinical Research
Department of Neurosurgery
Thomas Jefferson University
P: 215-955-7301
July 2013 – March 2014


## 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.

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

### 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.

<table>
<thead>
<tr>
<th>When</th>
<th>Second Thursday of every month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time</td>
<td>7-8:30 p.m.</td>
</tr>
<tr>
<td>Place</td>
<td>Jefferson Hospital for Neuroscience, 3rd Floor conference room 900 Walnut Street</td>
</tr>
<tr>
<td></td>
<td>Philadelphia, PA 19107</td>
</tr>
<tr>
<td>Facilitator</td>
<td>Joseph McBride, BSN, RN and Katelyn Salvatore, BSN, RN, 215-955-4429</td>
</tr>
<tr>
<td>Information</td>
<td>Light refreshments and snacks will be served. Free parking is available at the Jefferson Hospital for Neuroscience parking lot</td>
</tr>
</tbody>
</table>

### Neurosurgical Emergency Hotline

Jefferson Hospital for Neuroscience  
Aneurysms • AVMs • Intracranial Bleeds  
7 day • 24 hour coverage  
1-866-200-4854
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 neurological 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

Fridays, 7:00 am
De Palma Auditorium
1025 Walnut Street
College Building, Basement
Philadelphia, PA 19107

SAVE THE DATE

26th ANNUAL PAN PHILADELPHIA NEUROSURGERY CONFERENCE
DECEMBER 5, 2014

THE UNION LEAGUE OF PHILADELPHIA ● PHILADELPHIA, PA
Jefferson Hospital for Neuroscience is the region’s only hospital dedicated to neurosurgery and neurology, with specialized critical care units and advanced technology. The experience of our physicians – including six board-certified neurointensivists – and nurses is nearly impossible to match, especially when it comes to treating brain aneurysms, AVMs, brain tumors and stroke with minimally invasive procedures they helped to develop. For neuroscience, experience the advantages that choosing our team makes. Choose Jefferson.