VOL 10, ISSUE 1 | Winter 2015

JHN JOURNAL

a publication of Thomas Jefferson University, Department of Neurological Surgery

Decompressive Hemicraniectomy for Ischemic Stroke • Stereotactic Radiosurgery for Cavernous Malformations • Systemic Non-Langerhans Histiocytosis Student Interest in Neurosurgery • Anterior Temporal Lobectomy

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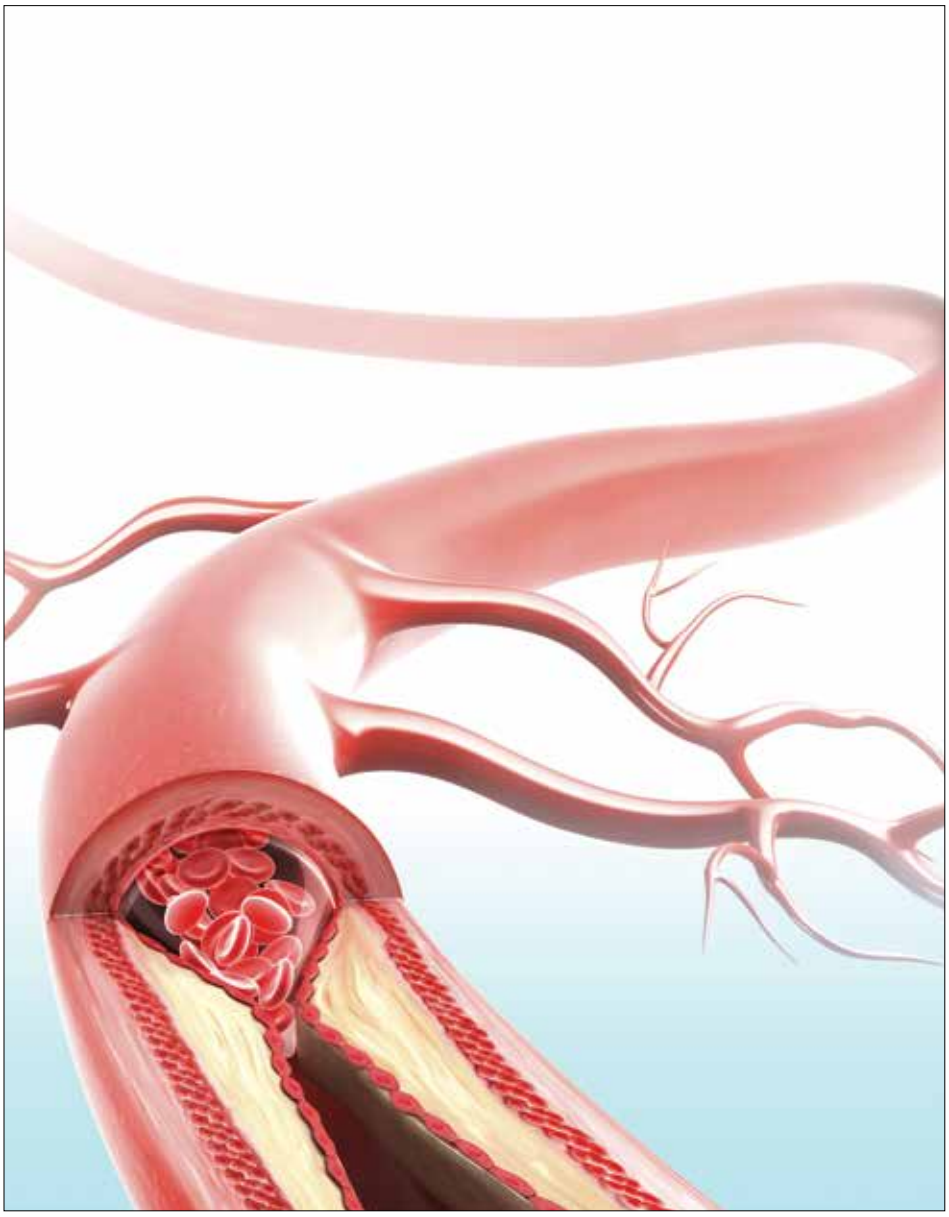

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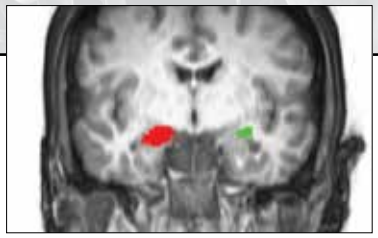
Correspondence, inquiries, or comments may be submitted to the Editor, JHN Journal, 909 Walnut Street, 3rd Floor, Philadelphia, PA 19107 or email at JHNjournal@jefferson.edu

 ISSN 1558-8726

CS 15-0392



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Decompressive Hemicraniectomy: Predictors and Functional Outcome In Patients With Ischemic Stroke

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BACKGROUND

Patients presenting with large ischemic strokes may develop uncontrollable, progressive brain edema that risks compression of brain parenchyma and cerebral herniation.[1] Edema that does not respond to medical treatment necessitates decompressive hemicraniectomy (DH) as a life-saving procedure. The functional outcome of patients is uncertain and the patient's family is presented with the difficult decision of intervention with DH. While the functional outcome of patients is not worsened by DH,[2] neurological deficit is likely as a result of initial large-territory ischemia. The correlation of specific clinical variables preceding DH to patient outcome helps inform clinicians and families about prognosis.[3] This study identifies an array of clinical variables in patients who underwent DH for ischemic stroke in order to investigate potential predictors of functional outcome.

METHOD

A total of 1,624 subjects that underwent any type of craniectomy from 2006 to 2014 were retrospectively screened via electronic medical record. The specific selection criterion was DH secondary to ischemic stroke involving the middle cerebral artery (MCA), internal carotid artery (ICA), or both. Subjects were excluded if they underwent craniectomy for any reason other than DH for ischemic stroke; or if the MCA or ICA were not implicated. The clinical variables that were collected may be divided into pre-DH and post-DH. The pre-DH variables involve patient demographics and past medical history, in addition to clinical variables during the period of presentation and clinical management leading up to DH. The post-DH variables describe the in-patient recovery period and discharge status. The primary outcome was functional status assessed by the Modified Rankin Scale (MRS) score at 90 days post-DH. The MRS ranges from 0 (no symptoms) to 6 (death) with intermediate values (1-5) representing increasing functional and cognitive disability.

RESULTS

There were N = 95 subjects who presented with ischemic stroke involving the MCA (72%), ICA (7%), or both MCA+ICA (21%) and underwent DH. Mean age was 57 $\pm$ 12 years, 60% were male, and the mean BMI was 28.3 $\pm$ 7.4 kg/m2. Atrial fibrillation was diagnosed in 25%, hypertension 80%, and prior stroke 20% of subjects. The mean National Institutes of Health Stroke Scale (NIHSS) score was 16 $\pm$ 5. Tissue plasminogen activator (tPA) was administered in 29% of subjects and 19% underwent endovascular intervention prior to DH. The mean peak midline shift was 9 $\pm$ 5 mm. Time from stroke onset to DH was 3 $\pm$ 3 days. Tracheostomy was performed in 36% and percutaneous endoscopic gastrostomy (PEG) 63% of subjects. An IVC filter was placed in 25% of subjects. Overall, subjects were hospitalized for 22 $\pm$ 17 days. The mean MRS score at 90 days post-DH was 4 $\pm$ 1 characterized as moderately severe disability. Mortality (MRS = 6) at 90 days post-DH was 18%.

DISCUSSION

Background

The present analysis describes the clinical variables and functional outcome in patients who underwent DH subsequent to severe cerebral edema that resulted from ischemic stroke. The characteristic patient was male, clinically overweight with a history of hypertension, and presenting with an NIHSS > 10 implicating the right MCA. Cases involving intervention with tPA or endovascular therapy did not preclude the need for DH. The midline shift is serially monitored by neuroradiology for patients with cerebral edema. The peak value was collected, with a mean shift of 9 mm prior to intervention with DH. Although the mean time from stroke onset to DH was 3 days, it was possible for DH to occur at a max of 35 days. Depending on the severity of stroke patients required tracheostomy for ventilator assistance, and PEG tube placement to provide a route for adequate nutrition. The incidence of deep vein thrombosis (DVT) and requirement for placement of an IVC filter was not uncommon during the in-patient recovery period, which is likely related to venous blood stasis and comorbidity in the setting of prolonged immobilization. After total hospitalization for nearly a month subjects were typically discharged to a rehabilitation center or nursing home. At 90 days post-DH most patients had disability requiring assistance (MRS 3 - 5), a minority of patients (4%) were considered functionally independent (MRS = 2), and 18% of patients

Table 1: . Patient Characteristics			
Demographics/comorbidities	**N=95**	**Percent (%)**	
Gender			
Males	57	60	
Females	38	40	
Age (yr) – Mean (max/min)	**Mean**	**Max**	**Min**
	57 ± 12	88	22
BMI (kg/m^2)	28.6 ± 7.4	66.9	14.5
Comorbidities			
Smoking	37	39	
Atrial Fibrillation	24	25	
Hypertension	77	81	
Hyperlipidemia	39	39	
Diabetes	31	33	
Myocardial Infarction	13	14	
Seizures	12	13	
Past Strokes	19	20	

Table 2: Subject stroke presentation characteristics		
Infarct Site		**N=95 (%)**
Middle Cerebral Artery (MCA	Right	43 (46)
	Left	21 (22)
	Bilateral	4 (4)
Internal Carotid Artery (ICA)	Right	2 (2)
	Left	3 (3)
	Bilateral	2 (2)
MCA + ICA		20 (21)
Intervention	**Yes (%)**	**No (%)**
tPA Administered	28 (29)	67 (71)
Endovascular intervention	18 (19)	77 (81)
Clinical Parameters	**Mean**	**Max/Min**
Midline shift (mm)	9 ± 5	19/0
NIHSS	16 ± 5	32/1
Time onset to DH (days)	3 ± 3	35/0

Table 3: Subject outcomes			
	Yes (%)	**No (%)**	
Tracheostomy	35 (36)	61 (64)	
Gastrostomy	60 (63)	33 (35)	
IVC filter	24 (25)	71 (75)	
	Average	**Max**	**Min**
Hospital stay duration (days)	22 ± 17	101	3
Modified Rankin Scale (MRS) score, 90 days post-DH	4 ± 1	6	2
	Yes (%)	**No (%)**	
Mortality, 90 days post-DH	17 (18)	78 (82)	

were deceased (MRS = 6). An MRS of 0 (no symptoms) or 1 (no disability despite symptoms) was not observed. The relationship of clinical variables to functional outcome will be investigated further in a secondary analysis. Identifying or ruling out such relationships might prove beneficial to clinicians and families in estimating functional outcome for individual patients prior to performing DH.

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Stereotactic Radiosurgery for Management of Cavernous Malformations

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Cavernous malformations (CMs) are abnormal vascular formations of the brain with an estimated incidence of 0.4%-0.8% in the general population.[1] CMs have the potential to cause significant morbidity, and have been associated with epileptic seizures, intracranial hemorrhage, and focal neurological deficits.[2] Management options include non-treatment, surgical resection, and radiosurgery. We review here the efficacy of different management strategies for cavernous malformations and highlight the specific role of radiosurgery.

One of the major complications of cerebral cavernous malformations is intracranial hemorrhage. To optimize patient treatment, it is beneficial to be able to identify patients that are at an increased risk of developing a hemorrhage and would most benefit from intervention. The overall rate of hemorrhage in patients with CMs has been estimated to be 2.25%.[3] The rate of hemorrhage, however, is significantly affected by the initial symptom presentation. Patients presenting with a hemorrhage have significantly higher rates of rehemorrhage compared to patients presenting due to incidental findings.[3,4] Flemming et al. found that patients presenting with hemorrhage had an overall annual rate of hemorrhage of 6.19% compared to patients presenting without hemorrhage of 0.33%. With increasing use of MR imaging, the percentage of cavernous malformations found incidentally approaches 40%.[1] Because the risk of hemorrhage is low in patients with CMs found incidentally, surgical or radiosurgery management may not be indicated. In contrast, patients presenting with symptoms of hemorrhage should be considered for therapeutic intervention due to a high risk for subsequent hemorrhage.

One option for the management of cavernous malformations is surgical intervention by CM resection. There is conflicting evidence in the literature regarding the effectiveness of CM resection, likely due to different methodologies used for determining efficacy. When post-operative outcomes are compared to pre-operative values, significant improvement is observed as demonstrated by improvements in the modified Rankin scale and decreased annual hemorrhage rate.[5,6] However, the results are limited by the fact that studies did not include a control group of patients that did not receive surgery. A recent retrospective study by Moultrie and colleagues compared the outcome of patients treated with surgical to conservative management. Patients who underwent CM resection had worsened short-term disability scores, increased risk of developing intracranial hemorrhage, and new focal neurologic deficits.[7]

While these results question the utility of surgical resection for management of cavernous malformations, there are situations in which CM resection may be beneficial. CM resection may be indicated in patients experiencing significant symptoms secondary to a cavernous malformation. For example, surgical resection has been found to significantly decrease seizures in CM patients presenting with epileptic seizures.[8,9] Similarly, patients with cavernous malformations in the brainstem experiencing significant symptoms (cranial nerve deficits, headaches, ataxia) have significant relief of their symptoms from minimally invasive resection, provided the CM can be accessed with minimal tissue pertubation.[10] Overall, it is clear that there are limitations to surgical treatment of cavernous malformations. Surgical resection should be reserved for easily accessible cavernous malformations in patients experiencing significant symptoms. For deeper-seated malformations, alternative treatment such as radiosurgery should be explored.

Stereotactic radiosurgery is an appealing alternative to surgical resection because it is minimally invasive and lacks immediate morbidity.[11] Radiosurgery is believed to induce a hyalinization and thickening of blood vessels resulting in luminal closure, or a thrombotic process in which shunting can no longer occur.[13,14] In contrast to surgical resection, resolution of the cavernous malformation can take up to two years. Radiosurgery is generally reserved for treating cavernous malformations which are in eloquent and difficult to reach locations considered high risk for microsurgery. Approximately 20% of cerebral cavernous malformations are located in the brainstem region, demonstrating the need for minimally or non-invasive therapy.[6] In spite of its appeal, conservative management is still recommended until the cavernous malformation has bled twice, or is at significant risk for bleeding.[12]

Evidence suggests that patients with a high risk of hemorrhage would benefit most from stereotactic radiosurgery. Nagy et al. determined the annual hemorrhage rate for a single symptomatic, or asymptomatic bleed to be 2.4% before radiosurgical treatment, 5.1% in the two years after treatment, and 1.3% beyond two years. These findings suggest that in patients with asymptomatic CM, the risk of morbidity is different whether looking at short or long-term follow-up. Compared to conservative management, patients have a higher risk of morbidity the first two years after radiosurgical treatment. However, after two years the risk of morbidity is significantly decreased. In contrast, the risk for additional bleeds may be as high as 40% for patients that have had one previous symptomatic bleed.[11] Radiosurgery is considered to be effective for high risk CM patients. Nagy et al. found that the rebleeding rate went from 30.5% before treatment to 15% in the first two years and further fell to 2.4%

beyond two years.[11] Evidence in support of radiosurgery for high risk symptomatic patients is compelling, yet there is not a significant body of evidence supporting radiosurgery for incidental CMs.

The lack of randomized controlled studies, and a paucity of long term effects and safety data has limited the quality of evidence relating to radiosurgery, and so its indications and effectiveness are still debated.[2] Consequently, although SRS may be beneficial for surgically inaccessible CMs with a high risk for rebleed, it is rarely used. Patients who do not have a history of more than one significant bleed should undergo conservative management rather than SRS because of the significant risk of post-SRS bleeding for up to two years.[13]

Dose of radiation is also an important consideration when determining whether or not to use radiosurgery. In attempt to reduce the radiation-related sequelae in eloquent locations, some surgeons have reduced the dose of radiation used to treat cavernous malformations.[11] A significant concern with the reduction in radiation dose is whether or not the radiosurgery is effective at a lower dose. Current imaging studies are unable to demonstrate whether or not radiosurgery is effective, and consequently all studies are based on clinical outcomes.[12] Many studies have examined the safest, and most effective mean tumor margin dose for proper obliteration of the CM and determined it to be between 12 and 16 Gy.[15] Lunsford et al. found that their mean marginal dose of 16 Gy resulted in adverse radiation effects in 11.65% of their radiosurgically treated patients, and Pollock et al. reported adverse radiation effects in 59% of patients with a mean marginal dose of 18 Gy.[13,16] These studies highlight the significance of adverse effects that can occur with radiosurgery, and make the decision to treat a radiosurgically eligible incidental cavernous malformation more difficult, especially taking into consideration the eloquent areas involved.

Seong-Hyun Park and Chalouhi both suggest that radiosurgery is an alternative to microsurgery for treating patients with CMs in high-risk areas who are symptomatic and at risk for future bleeds.[15,17] The decision for radiosurgical intervention in asymptomatic patients with incidental cavernous malformations is a complex issue. Cavernous malformations have variable courses. Some may remain relatively benign, but others may bleed and cause significant neurological deficit. Current guidelines suggest that asymptomatic CM patients should be followed with serial imaging studies and periodic clinical exams to continually assess whether or not intervention is warranted.[12]

Additional research is needed to fully understand the utility of radiosurgery for treating cavernous malformations. Patients with high-risk or symptomatic cavernous malformations appear to benefit most from radiosurgery. The role of radiosurgery in treating incidentally found cavernous malformations is less clear. A randomized controlled trial comparing radiosurgery to conservative management would be most beneficial.

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A Rare Case of a Systemic Non-Langerhans Histiocytosis Presenting with Diabetes Insipidus and a Tentorial Mass

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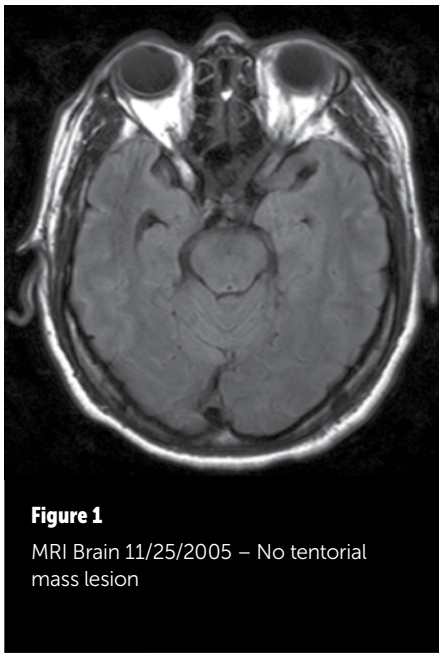


Figure 1
MRI Brain 11/25/2005 – No tentorial mass lesion

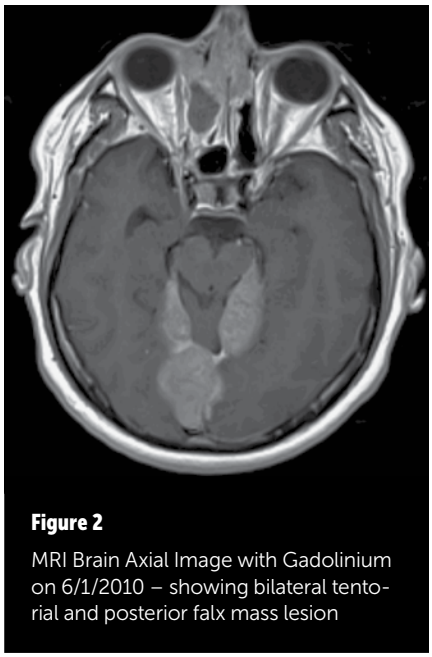


Figure 2
MRI Brain Axial Image with Gadolinium on 6/1/2010 – showing bilateral tentorial and posterior falx mass lesion

INTRODUCTION

The histiocytoses are a group of clinically diverse diseases distinguished from one another based on the specific immunophenotype of the lesional cells, implying derivation from the same precursor cell. Langerhans cell histiocytoses (LCH) diseases stem from abnormal dendritic cell lineages, while the non-Langerhans cell histiocytoses (non-LCH) are usually derived from an abnormal monocyte/macrophage cell line.[1] Non-LCH with central nervous system (CNS) involvement is predictive of poor outcome. Histopathology is used to make a diagnosis of non-LCH. Immunohistochemistry and the clinical setting are used to differentiate between the various subtypes of non-LCH.[1] The non-LCH can be divided into cutaneous non-LCH, cutaneous with a major systemic component, and systemic non-LCH.[1] Erdheim-Chester disease (ECD) and Rosai-Dorfman disease (RDD) are systemic non-LCH diseases.

First described in 1930, ECD is characterized by xanthogranulomatous accumulations. The extent of infiltration is heterogeneous and can include skin, bones, lungs, kidneys, and the CNS. Approximately 500 cases have been reported so far.[2] The majority of ECD patients harbor an activating mutation of the proto-oncogene BRAF, namely BRAF-V600E.[3] Recent studies indicate CNS involvement as a predictor of highest mortality among ECD patients.[4]

First described in 1969, RDD is characterized by accumulation of histiocytes exhibiting emperipolesis in lymph nodes, in the head and neck or in extranodal sites. Extranodal sites include the CNS, skin, soft tissue and gastrointestinal tract. The clinical presentation is typically painless cervical lymphadenopathy with leukocytosis and a fever.[5] The etiology of RDD is unknown.[6] RDD with CNS involvement is rare and approximately 210 cases have been reported. CNS involvement typically lacks extracranial lymphadenopathy and resembles meningioma radiologically and clinically.[1] Select cases have demonstrated a combined presentation of ECD and RDD.[2]

In this report we describe a rare case presenting with headache and with clinically and pathologically overlapping features of RDD and ECD. We describe treatment and complications and review the existing literature regarding diagnosis and treatment for these rare conditions.

CASE REPORT

The patient is a 46-year-old gentleman from Mexico who was initially admitted to the Neurology service at Jefferson Hospital for Neuroscience in November 2005 with headache, vertigo, nausea and vomiting and was found to have bilateral vertebral artery dissection with proximal basilar artery thrombosis (MRI Picture, Figure 1). He was started on anticoagulation and discharged home. In June 2010 he presented to the neurosurgery office with worsening headaches and a MRI of the brain showed bilateral tentorial and posterior falcine mass suggestive of meningioma (MRI Picture, Figure 2). The mass was surrounding the incisura.

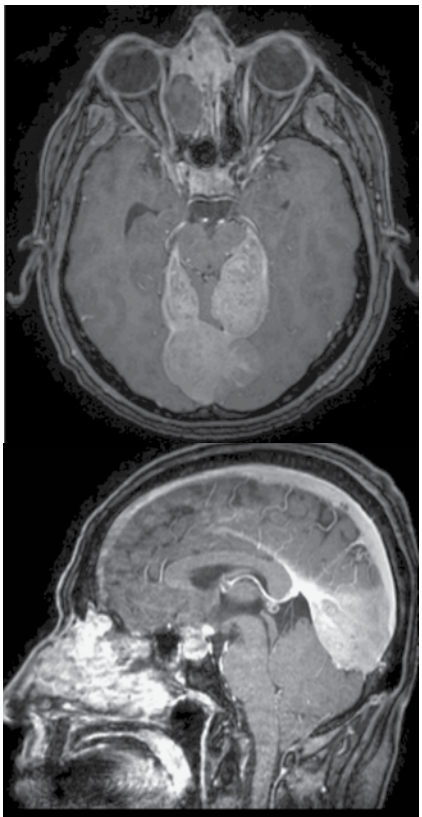
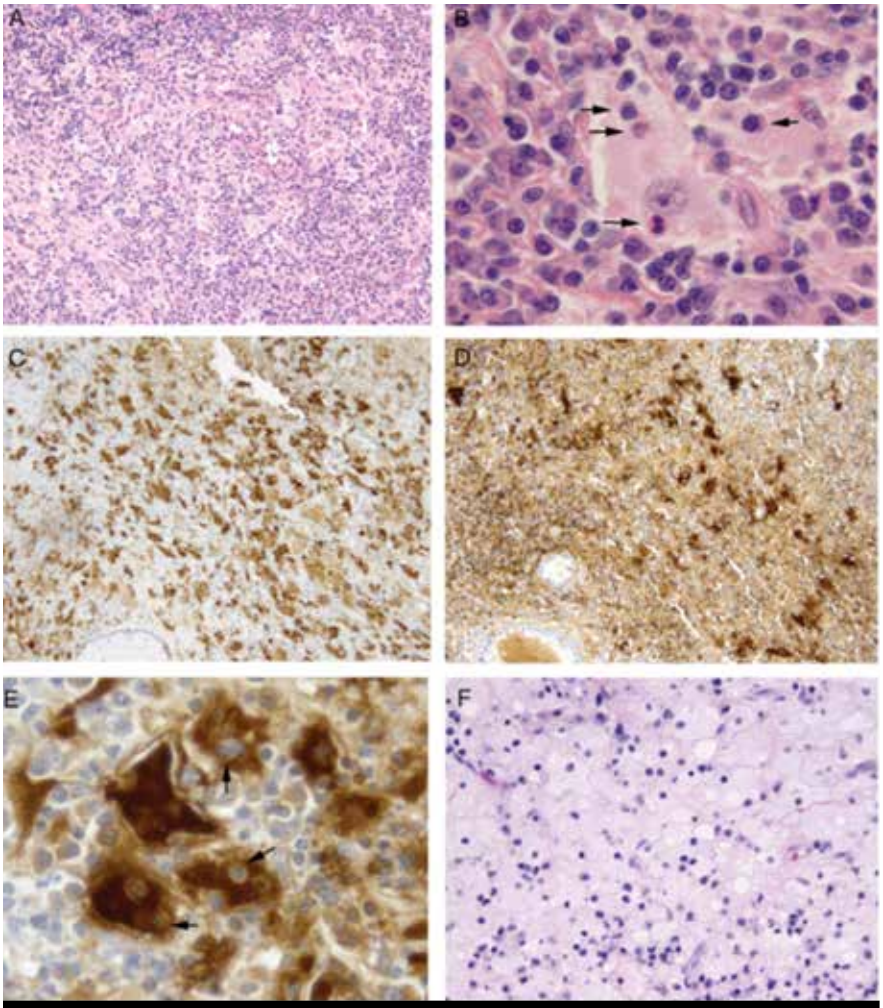


Figure 3

MRI Brain Axial Image with Gadolinium 7/25/2011- showing progression of b/l tentorial and posterior falx mass lesion

MRI Brain Sagittal Image with Gadolinium 7/25/2011 – showing sinonasal and sellar mass lesions



Path Slide 1

First operation A-E. A. Inflammatory infiltrate composed of lymphocytes, plasma cells, and histiocytes (Hematoxylin and Eosin, 200X). B. High magnification (Hematoxylin and Eosin, 1000X) demonstrates a typical Rosai-Dorfman histiocyte with neutrophils and plasma cells undergoing emperipolesis (arrowed). C,D. The histiocytes are strongly immunoreactive for CD163 (200X) and S-100 (200X) respectively. E. High magnfication (1000X) confirms the presence of emperipolesis (arrowed) within S-100 immunoreactive histiocytes. F. Second operation, sheets of foamy macrophages without emperipolesis (H&E, 400X). mass lesions

He also had an enhancing lesion in the ethmoid sinus. He was recommended to have a procedure for tissue diagnosis but he failed to do so and was lost to follow up.

In July 2011 he represented to the Jefferson Hospital ER with worsening symptoms and new onset diabetes insipidus. MRI brain, MR angiogram and CT sinus showed progression of the tentorial mass and a new sellar mass in the region of the pituitary gland and extensive sinonasal soft tissue mass extending into the right orbit (MRI Picture, Figure 3). On 7/28/2011 he underwent endoscopic transnasal transsphenoidal resection of the sinonasal and sellar mass. He also had an enhancing lesion in the ethmoid sinus. He was recommended to have a procedure for tissue diagnosis but he failed to do so and was lost to follow up.

The lesion consisted of an inflammatory infiltrate composed of lymphocytes, plasma cells and histiocytes (path slide 1A). High magnification images demonstrated intact inflammatory cells within the cytoplasm of many of the large histiocytes (path slide 1B). This phenomenon, known as emperipolesis, is characteristic of Rosai-Dorfman Disease. These histiocytes were immunohistochemically positive for macrophage markers CD68 and CD163 (path slide 1C) as well as S-100 (path slide 1D, E), but were negative for CD1a. This immunophenotype is typical of Rosai-Dorfman histiocytes. In contrast, macrophages and Erdheim-Chester histiocytes are immunoreactive for CD68 and CD163

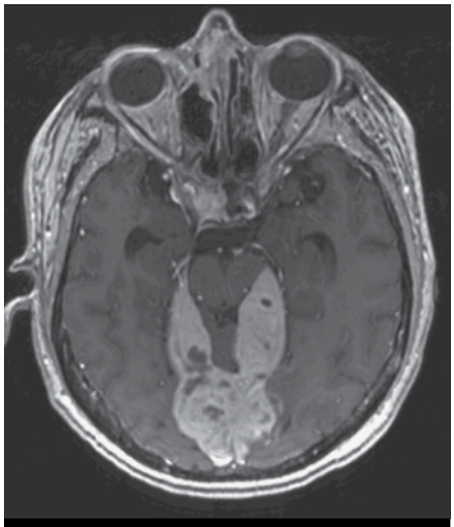


Figure 4

Pre Op MRI Brain Axial Image with Gadolinium 5/19/2012 – showing infratentorial and supratentorial mass

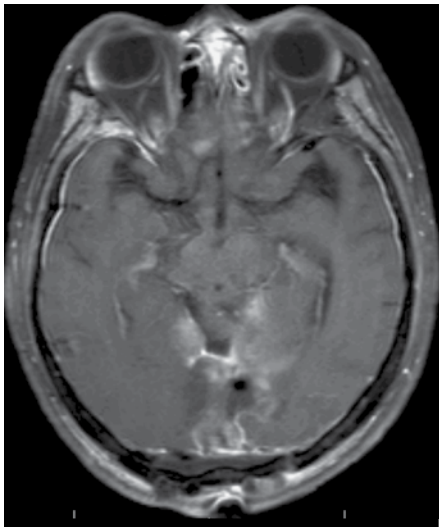


Figure 5

Post Op MRI Brian Axial Image with Gadolinium 5/26/2012 – showing gross total resection

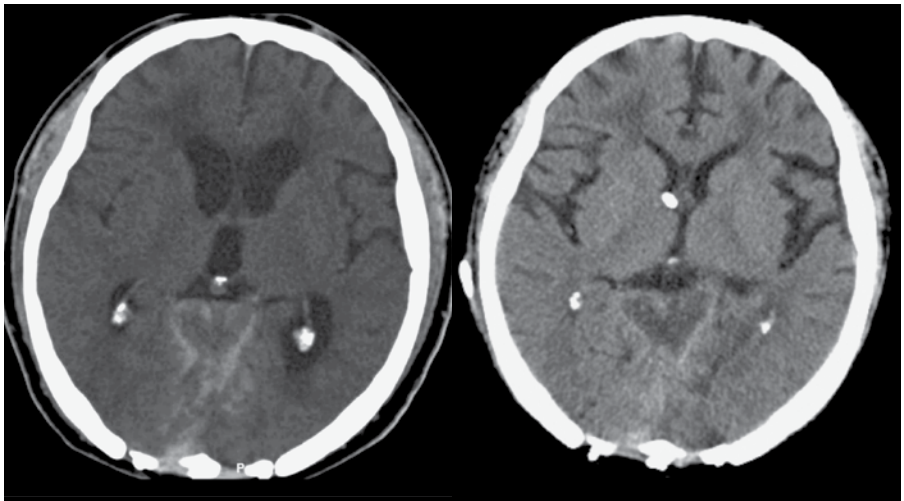


Figure 6

CT head without contrast 9/26/2014- showing hydrocephalus

CT head without contrast 10/04/2014 – post op after VP shunt showing resolution of hydrocephalus

but negative for S-100 and CD1a. Langerhan's cell histiocytes are immunoreactive for CD68, CD163, S-100, and CD1a. While the resection's pathology was consistent with RDD, the chest, abdomen and pelvis done to rule out systemic disease showed pulmonary interstitial thickening with fibrotic changes and the perinephric fat stranding consistent with ECD.

During the same hospitalization he developed left ureteroplevic junction obstruction and hydronephrosis requiring stent placement.

He was discharged to rehab with outpatient follow up. From 8/29/2011 to 9/14/2011 he completed radiation therapy of 24 Gy in 12 fractions to the paranasal sinuses and whole brain. In December 2011 he was started on interferon alpha and had vast improvement of his symptoms.

In May 2012 he was readmitted with worsening headache and vision, on exam he had left homonymous hemianopia. MRI of the brain showed progression of the tentorial mass, compressing the occipital lobes bilaterally (MRI Picture, Figure 4). He was taken to the operating room and underwent an occipital/suboccipital craniotomy. A near total resection of a solid avascular mass arising from the tentorium was performed using a combined supratentorial and infratentorial approach. Post-operative MRI of the brain confirmed minimal residual on the right aspect of the tentorium and posterior falx (MRI Picture Figure 5).

Pathology from this resection was characteristic of ECD, revealing large numbers of foamy macrophages (path slide 1F) with foci of necrosis and cholesterol clefts. There was no evidence of emperipolesis and these macrophages/histiocytes were immunoreactive for CD68 and CD163, but negative for S-100 and CD1a. This immunophenotype is distinctly different from the original resection, and with the patient's clinical picture and multisystem involvement, points towards ECD. His headaches improved, and he was subsequently discharged home.

On June 12, 2012 he was admitted with an episode of unresponsiveness and was found to have a MRSA pneumonia with presumed sepsis. In the course of this hospitalization he was found unresponsive and in ventricular fibrillation. A cardiac catheterization revealed non-occlusive coronary artery disease and he underwent implantable cardioverter-defibrillator placement on 6/27/12.

By June 2013 his diabetes insipidus had resolved and overall he was feeling much better. He was lost to follow up since he returned to Mexico, however he presented in September 2014 with headache, gait

ataxia (right greater than left cerebellar dysmetria), left homonymous hemianopsia and on non-contrast head CT was found to have progressive communicating hydrocephalus. On 9/29/2014 he underwent a right ventriculoperitoneal shunt placement for relief (CT head pre and post VP shunt, Figure 6). CT head with contrast showed some recurrence of the tentorial mass (CT head with contrast, Figure 7) He recovered well enough and was discharged to rehabilitation unit.

DISCUSSION

ECD is a rare systemic non-LCH involving xanthogranulomatous infiltration of tissues by foamy histiocytes (lipid-laded macrophages) surrounded by fibrosis.[2] It is typically diagnosed in the fifth decade of life, with a mean age of 55, and is more prevalent in males than females. ECD is considered to be both a neoplastic and inflammatory disorder, as the disease associates with a specific oncogenic alteration in the form of the BRAFV600E mutation, as well as a characteristic inflammatory pattern of cytokines and chemokines.[7]

Although it is a clinically heterogeneous disease involving several organ systems, ECD patients most commonly present with bilateral osteosclerosis of long bones of the upper and lower extremities on CT scans.[8] Other associated systemic manifestations include pseudotumor of the right heart, pericardial fibrosis, "hairy kidney" due to infiltration into perinephric soft tissue, exophthalmos, pulmonary fibrosis, and CNS involvement.[2,9] Less than 50% of patients with proven ECD have neurologic involvement.[8] The most common neurological symptoms are diabetes insipidus and cerebellar issues, both of which are part of our patient's history.[10] Lesions in the CNS have been specifically identified in the hypothalamic-pituitary axis, cavernous sinus, orbits, paranasal sinuses, brainstem, and vertebral column.[8] The prognosis for patients with ECD is variable and depends on the extent of disease.[2,8] Renal failure, cardiomyopathy, and respiratory failure are the most common causes of death in patients with ECD.[8] 59% of patients succumb to ECD after a mean follow-up of 32 months.[11]

The definitive diagnosis for ECD can only be made via histopathology analysis and immunohistochemistry, with the presence of infiltrating foamy, lipid-laden histiocytes, characteristic multinucleated Touton-type giant cells, and fibrosis.[2,10] Cells are positive for CD68 and negative for CD1a.[12]

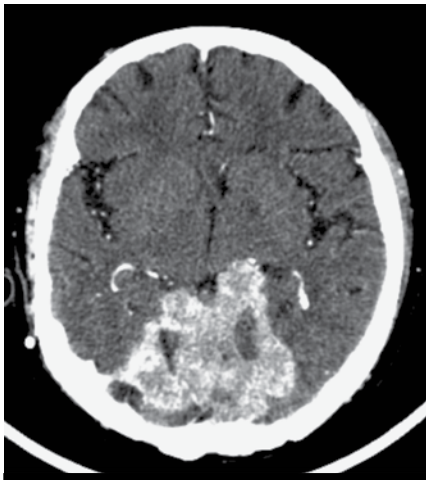


Figure 7

CT head with contrast 10/09/2014 – showing recurrence of infratentorial and supratentorial mass lesions

RDD is a nonmalignant non-LCH histiocytosis in which histiocytes infiltrate lymph nodes or extranodal tissues. RDD is typically diagnosed in the second or third decade of life and is more prevalent in African American individuals and in males compared to females.[5,13] Patients with RDD classically present with symptoms of fever and massive, nonpainful cervical lymphadenopathy. Some patients experience night sweats and weight loss as well as painless maculopapular eruptions.[5,14] Osteolytic bone lesions are rare in RDD, unlike in patients with Langerhans cell histiocytosis.[15] 20% of patients with RDD have spontaneous regression without treatment.[16] In patients without treatment, 70% will experience a relapsing and remitting course.[16]

Common sites for extranodal infiltration include the CNS, skin, orbit and eyelid, upper respiratory tract, and the gastrointestinal tract; some reports suggest extranodal involvement may occur in up to 40% of cases.[5] CNS involvement of RDD is commonly with dura-based, extra-axial involvement of the cranium; spinal cord and intracerebral disease are rare. Headaches and seizures are common as well as other neurological symptoms depending on the location of the lesion; constitutional symptoms are usually absent.[5]

To make a diagnosis of RDD, an excisional biopsy should be performed for immunohistochemical and morphological analyses.[5] The hallmark of RDD cells is emperipolesis or the nondestructive phagocytosis of lymphocytes or erythrocytes.[5] Cells will be positive for CD68 (KP-1), CD163, and S100 and are negative for CD1a.[5]

It is not uncommon for patients to present with both ECD and another form of LCH or non-LCH, as evidenced in 15% of 101 patients by Haroche et al.[2] Our patient presented in this case report falls into this category, concurrently expressing two systemic forms, ECD and RDD.

Treatment, both surgical and non-surgical, is similar for these two non-LCH diseases. For asymptomatic patients, it is recommended to observe, with close following of the disease for progression. However, for symptomatic patients with localized lesions, particularly in the CNS, surgical resection and/or radiotherapy is the treatment of choice. In a study involving 10 RDD patients with CNS involvement, 7 of them achieved remission at follow-up after surgical resection of the lesions.[17]

Interferon alpha (IFNα) therapy is the most studied,[7] and Haroche et al. recommends IFNα therapy as the initial treatment for patients with symptomatic ECD. In their survival analysis of 53 patients, treatment with IFNα was an independent predictor of survival.[2] High dose IFNα is most effective for CNS and cardiac involvement as Haroche et al. reported symptoms did not resolve in response to low dose IFNα. Side effects of IFNα can be intolerable and include fatigue and depression.[2] Other non-surgical treatments currently being investigated for ECD patients with a more disseminated disease including: methotrexate[18], canakinumab[19], vemurafenib (20), and interleukin-1 targeting drugs/glucocorticoids.[21] Vemurafenib, a BRAF inhibitor, has recently been utilized as an effective treatment for ECD patients harboring the BRAFV600E mutation with severe and refractory ECD, resulting in significant clinical improvement.[2,7]

Patients with RDD experiencing symptoms have nonsurgical treatment options such as radiotherapy, steroids or chemotherapy agents including vinca alkaloids and anthracyclines.[5] ECD and RDD are rare diseases and treatment options need to be studied further in randomized controlled trials in order to determine the best treatment for these patients.

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Student Interest in Neurosurgery: Review of the Literature and New Study at Sidney Kimmel Medical College of Thomas Jefferson University

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Neurosurgery is traditionally regarded as a highly competitive field attracting exceedingly qualified applicants.[1] However, the decision to pursue neurosurgery is challenging, and medical students can be discouraged due to lack of exposure to the field or inability to identify a mentor. Possible explanations for this decreased interest include concerns regarding work-life balance, inherent stress of the field, length of residency, and inadequate exposure to neurosurgery.[1-3] A recent medical student survey in Ireland showed that 70-100% of medical students felt that neurosurgery residency is too long, neurosurgical education at the medical student level is insufficient, neurosurgical patients have poor outcomes, and a career in neurosurgery impedes family life.[4] Concerns with manual dexterity and intelligence were demonstrated in a British medical student survey in addition to significantly decreased neurosurgery residency applications in comparison to other surgical specialty and radiological residencies.[5] Recent publications have indicated that improvement in neurosurgical rotations and recruitment of women into the field are significant issues.[3,6] However, it is of paramount importance for the field of neurological surgery to attract dedicated and bright medical students into this rigorous career path.

This decreased interest in the field has prompted a desire to explain the finding and improve recruitment. In 2002 the neurosurgery department at Rutgers instituted a four-phase initiative to improve neurosurgery recruitment.[2] The four phases of their study involved: earlier introduction of neurosurgery into third year clerkship, recruitment of undergraduate Rutgers students to participate in summer research projects, novel neurosurgical clerkships for third and fourth year medical students, and the establishment of a neurosurgical student interest group. The four phases took 10 years to complete and analysis indicated a dramatic increase in successful neurosurgical residency placements for Rutgers medical students.

Cardiothoracic surgery had also experienced a decline in residency applicants and this prompted a similar initiative at Johns Hopkins beginning in 2003 to increase medical student interest.[7,8] Their findings suggest that earlier exposure to cardiothoracic surgery and involvement of medical students in cardiothoracic research increases the number and quality of resident applicants.

A literature search reveals that there has been no prior survey of US medical students' perspective of neurosurgery and neurosurgery rotation. A new research project in the department of neurosurgery at Thomas Jefferson University (TJU) will gather third-year medical students' perspective of neurosurgery as a career choice and opinion of neurosurgery rotation at TJU. This survey will be significant because it will be the first of its kind and will have significant numbers due to the large number of medical students rotating through neurosurgery at TJU. The results of this survey will have both broad and local scope. The data will allow improved recruitment into neurosurgery nationally and also enhance neurosurgery rotation at TJU.

Through this survey of third year medical students after their neurosurgery rotation at TJU, we hope to demonstrate that early exposure and participation in the field promotes greater consideration of neurosurgery as a career. Students may not consider a specialty unless they have personal experience or an acquaintance within the specialty. This survey will allow us to investigate medical student views and concerns regarding a neurosurgery career and specifically the experience during the neurosurgery rotation at TJU. Some of the areas of potential concern for students addressed in the survey include: litigation, stress, work-life balance, salary, and family. Additionally, the survey will explore the positives and negatives of rotation at TJU. We hope this survey will allow us to both improve the rotation experience for third year medical students and foster passion in neurosurgery

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Emotional/Psychiatric Symptom Change and Amygdala Volume After Anterior Temporal Lobectomy

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INTRODUCTION

Patients who undergo anterior temporal lobectomy (ATL) to treat temporal lobe epilepsy (TLE) often experience worsened or de novo psychiatric symptoms. There is evidence to suggest that the pathophysiology of epilepsy and mood disorders are linked both functionally or structurally in the brain.[1,2] While several studies have examined the role that changes in hippocampal volume may play in predicting post-surgical depression, the role of the amygdala in such prediction has been overlooked, despite extensive literature demonstrating its contribution to emotion processing and expression.[3,4] The goal of this project was to determine if change in amygdala volume is a predictor of depression and/or anxiety in TLE patients who undergo ATL, with specific attention given to side of surgery.

METHODS

Data was collected from 32 patients who underwent ATLs (19 right, 13 left, matched samples). Pre- and post-surgery Personality Assessment Inventory (PAI) data were collected on 14 ATL patients. The following PAI subscales were utilized in this analysis: Anxiety: PAIANX; Anxiety Related Disorder: PAIARD; Depression: PAIDEP). Volumetric analysis was performed on pre- and post-surgical T1 MRIs using Freesurfer's longitudinal processing function. Left and right amygdala volumes, change scores, and amygdala asymmetry ratios were calculated taking into account whole brain volume. 55% of the patients were seizure-free after 1 year (RTLE= 8, LTLE= 9); 29% received an Engel Class score of 2 or 3 (RTLE= 7, LTLE= 2)

RESULTS

The two experimental groups, right TLE and left TLE, showed no significant differences either pre- or post-ATL: age, age of seizure onset, full-scale IQ or amygdala volume or asymmetry (Table 1).

Table 1: . Clinical and Demographics Characteristics of each TLE group

	RTLE	LTLE	Significant (?)
N (female)	18 (12)	13 (10)	NS
Age (years)	45 ± 12	48 ± 12	NS
Years of Education	15 ± 2	15 ± 3	NS
Time between surgery and Second Test (months)	15.4 ± 24.7	14.7 ± 16.2	NS
Age of seizure onset (years)	21 ± 11	25 ± 14	NS
L amygdala volume, pre-/post- surgery	0.18 ± 0.04/0.17 ± 0.04	0.17 ± 0.07/0.03 ± 0.03	NS/0.0
R amygdala volume, pre-/post- surgery	0.19 ± 0.06/0.03 ± 0.05	0.21 ± 0.08/0.17 ± 0.06	NS/0.0
Amygdala Asymmetry	0.03 ± 0.08/-0.73 ± 0.42	0.11 ± 0.06/0.62 ± 0.48	0.005/0.0
Psychiatric Scores, pre-/post- surgery			
PAIANX	57 ± 12/48 ± 6	53 ± 9/59 ± 13	NS/NS
PAIARD	53 ± 12/49 ± 12	51 ± 9/60 ± 16	NS/NS
PAIDEP	59 ± 11/54 ± 9	51 ± 7/64 ± 18	0.042/NS

All measures are shown as means ± standard deviation. Amygdala volume was calculated as a ratio with total gray matter volume. Amygdala was calculated as the difference between right and left maygdala volume rations over the combined right and left amygdala volume. Group comparisions were examined throug independent sample t-test. Abbreviations: Personality Assessment Inventory measures Anixiety (PAIANX), Anxiety Related Disorders Depression (PAIDEP).

Table 2: Post Surgical Psychiatric Scores. Results of regression analyses for PAIDEP, PAIANX, and PAIARD scores to amygdala volume, amygdala volume change, amygdala pre-surgery, and amygdala asymmetry change measurements. Significant results are marked with an asterisk.

Model	PAIDEP *Adj. R^2=0.64, F[7,15]=4.7, p=0.02*	PAIANX *Adj. R^2=0.56, F[7,15]=3.7, p=0.04*	PAIARD *Adj. R^2=0.6, F[7,15]=4.2, p=0.03*
	Stand. b Coef., p-value	**Stand. b Coef., p-value**	**Stand. b Coef., p-value**
ATL group	-0.24, .0.68	1.2, 0.08	0.57, 0.35
Left AMYG vol, pre-surg.	6.5, 0.008*	4.5, 0.06	5.8, 0.02*
Right AMYG vol, pre-surg.	-5.9, 0.02*	-4.2, 0.08	-5.2, 0.03*
Left AMYG vol change	-0.46, 0.72	-0.38, 0.79	-1.2, 0.38
Right AMYG vol change	4.4, 0.005*	2.5, 0.08	4.2, 0.009*
AMYG asym., pre-surg.	4.7, 0.02	3.2, 0.11	4.1, 0.04*
AMYG asym., change	-3.9, 0.04*	-3.5, 0.08	-5.3, 0.01*

Results of regression analyses for PAIDEP, PAIANX, and PAIARD scores to amygdala volume, amygdala volume change, amygdala pre-surgery, and amygdala asymmetry change measurements. Significant results are marked with an asterisk.

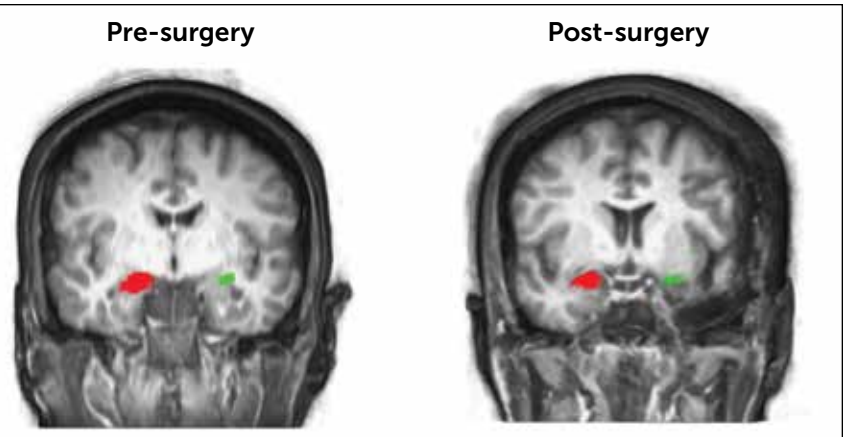


Figure 1

Pre- and post-surgery fMRI images from a Left TLE patient. The red and green overlays represent the right and left amygdala, respectively. The left temporal lobe resection is clearly visible in the right post-surgery image. Images shown in radiological view.

There is a change post-surgery in PAIANX (F[1,12]=6.6, p=.02), PAIDEP (F[1,12]=8.2,p=.01) and PAIARD (F[1,12]=4.5, p=.05; see Figure 2) that varies for both the left and right ATL groups, such that the RATL group symptom levels went down and LATL group levels went up.

Regression analysis showed that measures of amygdala volume, amygdala volume change, and amygdala asymmetry predict post-surgery PAIANX, PAIDEP, and PAIARD, explaining approximately 36% of the variance in each of these variables, though the individual beta coefficients were significant for only PAIARD and PAIDEP (Table 2). Examined within each ATL group, this regression model was only significant for PAIARD in the right ATL group.

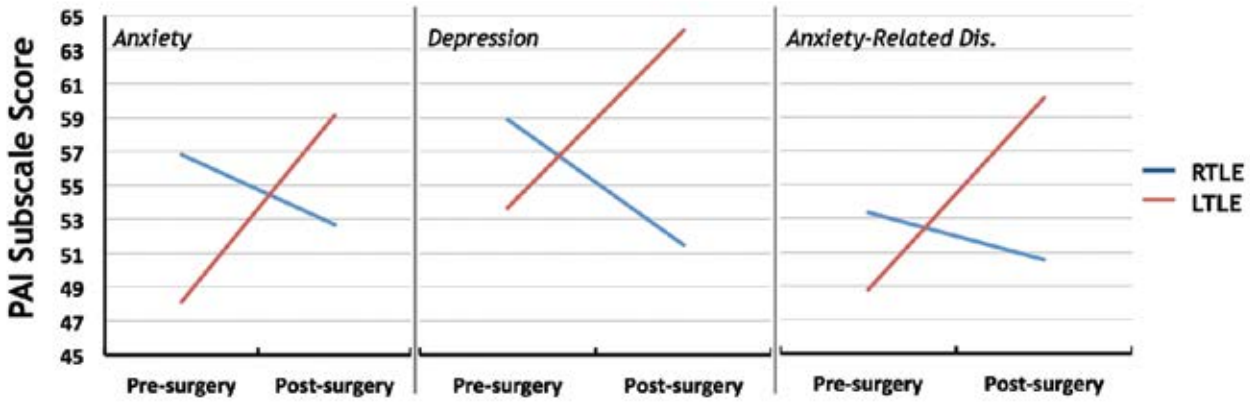
The above regression model remained significant when ATL group was included as a predictor, and also after accounting for pre-surgery PAI scores and age of seizure onset.

Correlational analyses showed that change in the ratio or asymmetry of right to left amygdala volume may result in post-surgical psychiatric symptom change in right but not left ATL patients, with loss of the right sided volume associated with decreases in PAIANX (r=-.77), PAIDEP (-.86), and PAI ARD (-.95).

CONCLUSIONS

Psychiatric symptoms changed in both left and right TLE, however, the direction of the effects differed. The left group consistently showed a worsening of symptoms. This suggests left more than right ATL disrupts emotion regulation systems, potentially placing patients at higher risk for deleterious post-surgical emotional/psychiatric change.

A multivariate combined model of amygdala volume, volume change, and asymmetry does predict post-surgical anxiety (rumination, tension), depression, and anxiety related disorders (phobia, trauma stress response). Increases in right



Figures 2: Comparision of Pre- and Post-Surgery PAI Subscale Scores in LTLE and RTLE Patients. Average pre-and post-surgical PAIANX, PAIDEP, and PAIARD scores plotted pre- and post-surgery. Psychiatric scores tend to decrease in RTLE patients post-surgery, whereas scores tend to increase post-surgery in LTLE patients.

amygdala volume and decreases in left amygdala volume related to higher levels of psychiatric symptoms post-surgery, but this effect needs to be retested in larger samples as it does not distinguish the separate effects in right and left ATL. There were some indications these associations with amygdala volume may be strongest with the PAI ARD variable in the right ATL group.

When viewing psychiatric symptoms alone, preliminary results suggest left ATL patients may fare worse post-surgery in terms of psychiatric symptoms. In contrast, associations with volume reveal that right ATL patients may be more sensitive to the ipsilateral amygdala loss than left patients, with reduction in this pathologic zone reducing levels of depression, anxiety, and anxiety/stress related symptoms.

The data suggest the catalyst of symptom change differs in the two ATL groups, with the left group more susceptible to causes less related to brain structure and more related to diminished dominant hemisphere functions (e.g., language/memory), and their negative impact on communication or vocational skills. In contrast, psychiatric symptom change in right ATL appeared more closely aligned with structural change (loss) in the ipsilateral amygdala, reducing pathologic emotion processing. An effect that may be related to the tendency for the right hemisphere to be dominant for emotion processing and regulation.

ACKNOWLEDGMENTS

This work was supported, in part, by the National Institute for Neurological Disorders and Stroke (NINDS) [grant number R21 NS056071-01A1] to Dr. Joseph I. Tracy

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An Update from the Division of Clinical Research

The Department of Neurological Surgery at Thomas Jefferson University is a national leader in neurosurgical research. The Department has 37 active clinical trials, 66 retrospective studies with 32 additional clinical trials in the pipeline.

The expanding research portfolio covers vascular and endovascular surgery, functional neurosurgery, spine and peripheral nerve surgery, oncological surgery, neuro-intensive care, and trauma.

The Department is staffed 24/7 by experienced clinical research nurses and coordinators to support ongoing research projects and to be available for emergent cases. A member of the research team can be reached any time at 215-964-4203.

Highlights

DIVISION OF NEUROVASCULAR SURGERY AND ENDOVASCULAR NEUROSURGERY

Principal Investigator: Pascal Jabbour MD
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Director, Division of Neurovascular Surgery and Endovascular Neurosurgery

Study title: Pivotal Study of the Microvention Flow Re-Direction Endoluminal Device Stent System in the Treatment of Intracranial Aneurysms

Short title: FRED

Funding agency: MicroVention

The FRED trial is a multi-site study to evaluate the safety and effectiveness of the FRED System when used in the treatment of large and giant wide necked aneurysms. FRED is a flow diverting stent used to treat large or giant wide neck intracranial aneurysms. Flow diverting stents are designed to redirect flow away from the aneurysm, thus allowing thrombosis to occur in the aneurysm. The FRED System consists of a self-expanding nickel titanium (nitinol) stent and a delivery pusher. FRED eliminates the need for the subject to have a craniotomy. The study will accrue 127 subjects from 25 sites across the country. Thomas Jefferson is one of the sites with a target enrollment of 7 subjects.

DIVISION OF NEURO-INTENSIVE CARE AND TRAUMA

Principal Investigator: Jack Jallo MD, PhD

Professor and Vice Chair for Academic Services
Director, Division of Neuro-intensive Care and Trauma

Study title: A Phase III, Randomized, Open-Label, 500 Subject Clinical Trial of Minimally Invasive Surgery plus rt-PA for ICH Evacuation

Short title: MISTIE III

Funding agency: Johns Hopkins University – National Institute of Neurological Diseases and Stroke/Genetech (drug supply only)

MISTIE III is designed to determine the efficacy and safety of an intervention to remove blood clot from brain tissue - without the need for craniotomy. MISTIE III uses a combination of minimally invasive surgery and clot lysis with rt-PA in the treatment of intra-cerebral hemorrhage. Image-based surgery is used to provide catheter access to clot for aspiration followed by instillation of rt-PA. MISTIE III will test if this intervention facilitates more rapid and complete recovery of function and decreased mortality compared to standard medical care. Five to ten subjects will be enrolled at Thomas Jefferson.

DIVISION OF SPINE AND PERIPHERAL NERVE SURGERY

Principal Investigator: James Harrop, MD

Professor
Director, Division of Spine and Peripheral Nerve Surgery

Study title: A Multi-Center, Randomized, Placebo-Controlled, Double Blinded, Trial of Efficacy and Safety of Riluzole in Spinal Cord Injury Study

Short title: RISCIS II

Funding agency: AOSpine, Christopher Reeves Foundation and the Department of Defense

RISCIS II is a Phase II/III clinical trial to evaluate if riluzole is superior to placebo in subjects with acute traumatic spinal cord injury. Riluzole is an anticonvulsant drug that exerts a neuro-protective effect by helping to maintain neuronal cellular ionic balance and by reducing the release of excitotoxic glutamate in post spinal cord injury. It is commonly used to treat amyotrophic lateral sclerosis. RISCIS II also evaluates the effects of riluzole on overall neurological recovery, sensory recovery, functional outcomes, quality of life outcomes, health utilities and mortality. This study is recruiting 351 subjects from 35 sites in and outside of the United States. Thomas Jefferson will accrue up to 20 subjects in this study.

DIVISION OF FUNCTIONAL NEUROSURGERY

Principal Investigator: Ashwini Sharan, MD

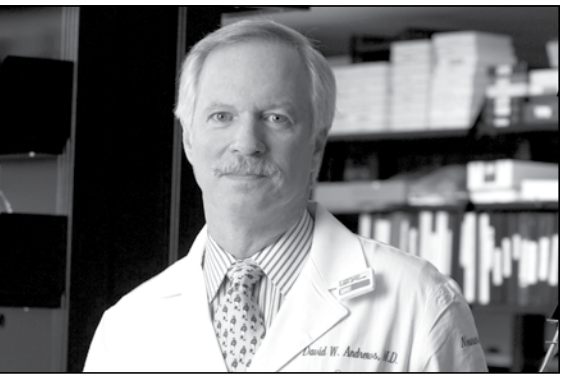
Professor
Director, Division of Functional Neurosurgery

Study title: A Prospective, Multicenter, Randomized, Double-Blinded Crossover Study Examining the Safety and Effectiveness of Using Spinal Cord Stimulation Incorporating Feedback to Treat Patients With Chronic Pain of Limbs in an Extended Trial

Short title: Panorama

Funding agency: Saluda Medical

Panorama compares the effectiveness of feedback and non-feedback spinal cord stimulation in patients with chronic pain with regard to pain relief and stimulation side effects (overstimulation or other unwanted changes in stimulation) in an extended trial. The External Trial System (ETS) developed by Saluda Medical provides feedback control during a trial of spinal cord stimulation (SCS) for subjects enrolled in the study. A stimulating and recording system is connected to SCS leads that the patient wears home from the clinic. A Clinic Interface (CI) system is used by the clinician to program stimulation and feedback parameters and to display and store information. During the test period of 20 days, the ETS feedback control system measures the electrical response from the nerve and uses this signal to control the stimulus amplitude from the stimulator. Panorama hopes to show that the ETS feedback control system is a safe and effective method of measuring electrical response from the nerves and that the system will effectively use this signal to control the stimulus amplitude from the stimulator – proving to be a more effective therapy. Seventy subjects will be enrolled nationally, with ten subjects enrolled at Thomas Jefferson.



DIVISION OF ONCOLOGICAL NEUROSURGERY

Principal Investigator: David Andrews, MD

Professor and Vice Chair for Clinical Services
Director, Division of Oncological Neurosurgery

Study title: Phase I Study in Humans Evaluating the Safety of Rectus Sheath Implantation of Diffusion Chambers Encapsulating Autologous Malignant Glioma Cells Treated with Insulin-Like Growth Factor Receptor -1 Antisense Oligodeoxynucleotide (IGF-1R/AS ODN) in Thirty Two Patients with Newly Diagnosed Malignant Glioma

Short title: Antisense 102

Funding agency: Investigator Initiated Trial

Antisense 102 in an investigator initiated single site, randomized trial to study the safety and effectiveness of IGF-1R/AS ODN (insulin-like growth factor receptor-1 antisense oligodeoxynucleotide) in subjects with newly diagnosed malignant glioma. The subject's tumor cells are harvested at surgery, treated ex vivo with the IGF-1R/AS ODN, encapsulated in diffusion chambers, and re-implanted in the subject's abdomen within 24 hours of craniotomy. Number of chambers and dwell time depends upon randomization to one of four cohorts. The IGF-1R/AS ODN targets the surface receptor protein allowing the combination product to serve as a therapeutic vaccine which activates an anti-tumor adaptive immune response. Thirty two subjects will be followed for 24 months for survival and radiographic assessment of their tumor.

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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.

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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

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.

When Third Wednesday of every month (September through June)

Time 6:30-8:30 p.m.

Place 900 Walnut Street, 3rd Floor, Conference Room
Philadelphia, PA 19107

Moderator/ Secretary Jill Galvao

Parking Complimentary parking is provided in the parking garage located in the JHN Building (Jefferson Hospital for Neuroscience) on 9th Street (between Locust & Walnut)

Information 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.

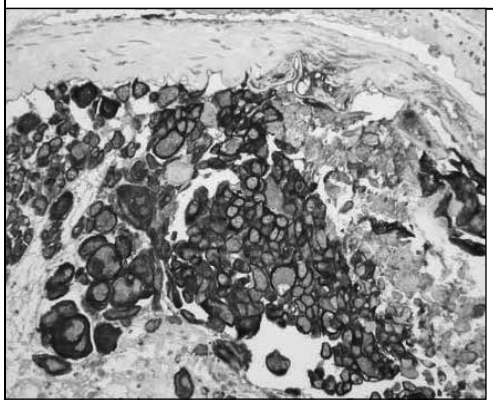
When Second Thursday of every month

Time 7-8:30 p.m.

Place Jefferson Hospital for Neuroscience, 3rd Floor conference room
900 Walnut Street
Philadelphia, PA 19107

Facilitator Joseph McBride, BSN, RN and Katelyn Salvatore, BSN, RN.
215-955-4429 or katlyn.salvatore@jefferson.edu

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



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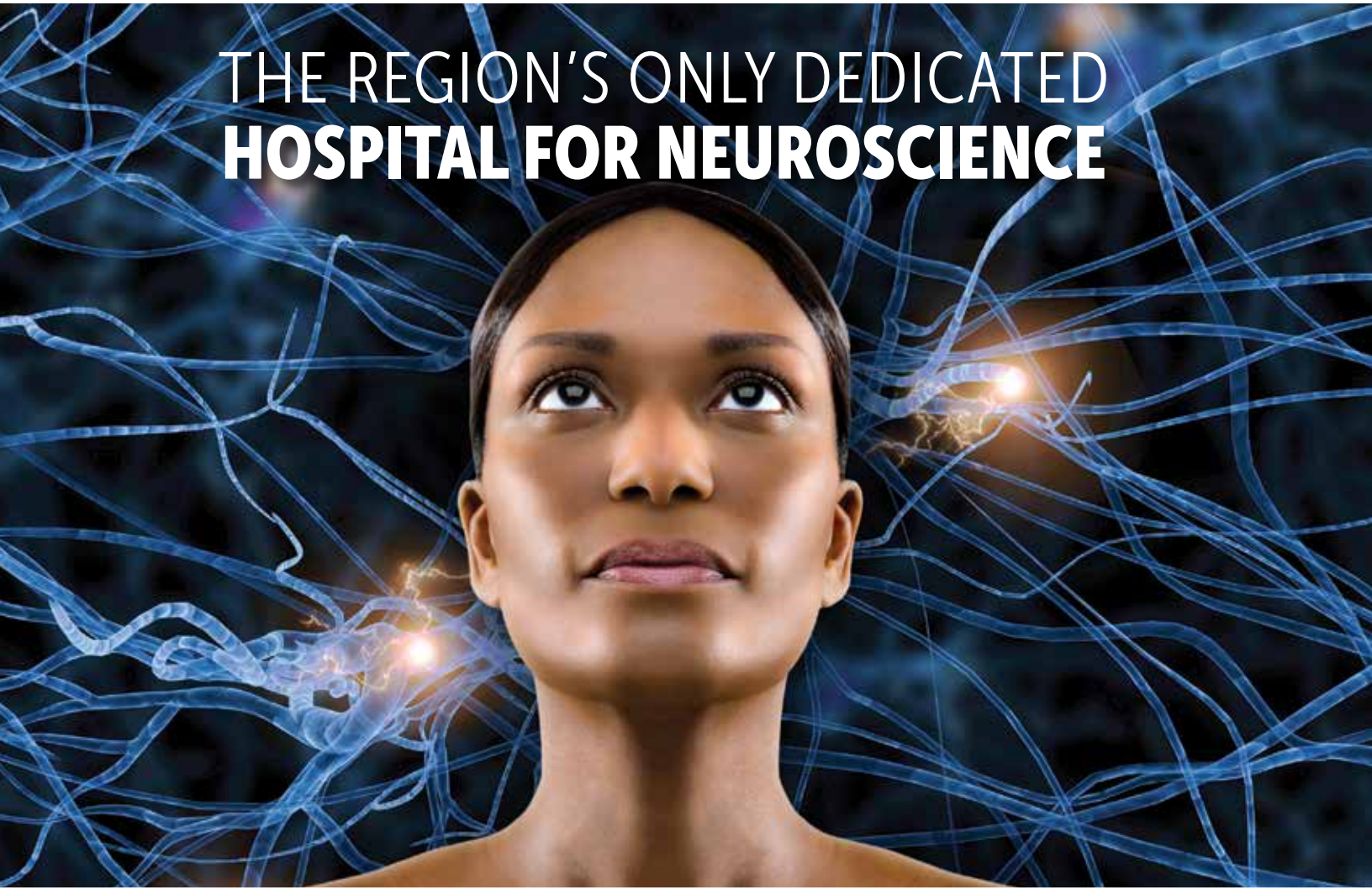

Jefferson Hospital for Neuroscience is the region's only hospital dedicated to neurosurgery and neurology, with specialized critical care units and advanced technology. The experience of our physicians – including six board-certified neurointensivists – and nurses is nearly impossible to match, especially 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.

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