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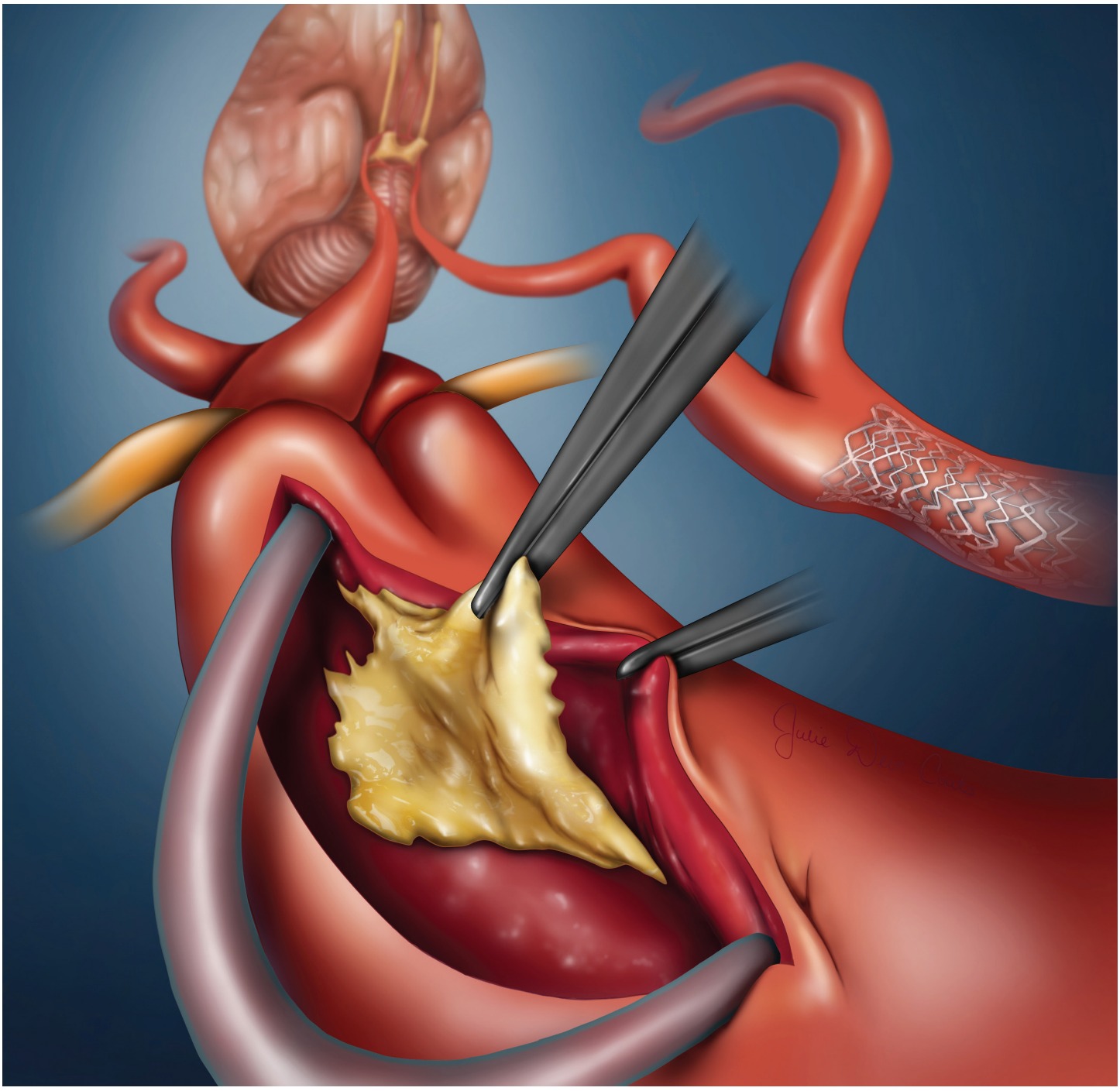

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UH Neurological Institute Journal

FROM THE EDITOR

Dear Colleague,

I am pleased to bring you the Fall 2015 issue of the UH Neurological Institute Journal.

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

This year's Fall issue begins with Fernando Alonso, MD, and colleagues reviewing treatment options for patients with carotid stenosis. They review the stroke risk associated with symptomatic and asymptomatic carotid stenosis and the role of treatment options – a matter of intense debate in need of further study.

Osmond Wu, MD, and colleagues present two cases and review the literature on pediatric thrombectomy for acute ischemic stroke. They discuss the unique decision-making and technical challenges associated with these procedures, as the etiology differs from that of adults. Though relatively uncommon, ischemic strokes in children appear to be increasing.

Mark Cohen, MD, and colleagues provide the first description of an infratentorial pleomorphic xanthoastrocytoma. The role of adjuvant therapies in such "collision tumors" is still unclear, but an increasing amount of data suggests that chemotherapy is not an effective adjuvant treatment and that resection provides an opportunity for a cure.

To wrap up the issue, Brian Appleby, MD, addresses the lack of consideration given to caregivers of Creutzfeldt-Jakob patients. He evaluates caregiver burden in Creutzfeldt-Jakob disease compared to other forms of dementia, emphasizing that psychiatric symptoms can be treated to help alleviate the burden.

We at the NI Journal extend our thanks to all of contributing authors as well as to our readers. Your comments and suggestions are always welcome.

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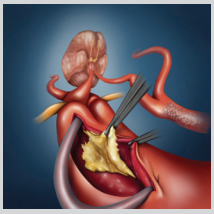

On the cover: *A carotid endarterectomy performed in the setting of symptomatic carotid stenosis for the prevention of ischemic stroke. Read more about this topic in the article by Fernando Alonso, MD, and colleagues on page 4. (Illustration by Julie Coats.)*

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Treatment of Symptomatic and Asymptomatic Carotid Stenosis: A Review of the Literature

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Introduction

It has been more than 60 years since Eastcott published the successful reconstruction of the internal carotid artery of a patient with intermittent episodes of hemiplegia.[1] Similarly, in 1953, Debakey performed the procedure in a patient suffering from hemispheric ischemic symptoms. The period from 1971 to 1985 saw an increase of carotid endarterectomies of 613 percent from 15,000 to 107,000 procedures per annum.[2-4] Without landmark studies analyzing the natural history and progression of carotid stenosis, the decision to operate was primarily based on a surgeon's individual experience. The North American Symptomatic Carotid Endarterectomy Trial (NASCET), first published in 1991, was a groundbreaking study as it clearly established the benefit of performing carotid endarterectomy on symptomatic patients with severe (70 to 99 percent) carotid stenosis.[4] NASCET also defined the method by which we continue to measure the amount of carotid stenosis, such that there is consistency among observers (Figure 1). The symptoms that can be associated with carotid stenosis are hemispheric in nature and include transient ischemic attacks, amaurosis fugax (temporary monocular blindness), and cerebral infarcts with neurologic deficits that last longer than 24 hours. Of note, however, in many carotid stenosis clinical trials, severe disabling strokes (Rankin score greater than or equal to 3) were excluded from enrollment. Treatment options for patients with carotid stenosis include optimal medical therapy, carotid endarterectomy, or carotid stent placement with or without angioplasty and with or without distal cerebral protection. In the following discussion, we review the stroke risk associated with symptomatic and asymptomatic carotid stenosis and the role of these three treatment options.

Symptomatic carotid stenosis

Initially, NASCET included patients who had a hemispheric or retinal transient ischemic attack or a nondisabling stroke with ipsilateral severe carotid stenosis (70 to 99 percent) within 120 days prior to entry to the study.[4] The two-year risk of ipsilateral stroke in patients with 70 – 99 percent carotid stenosis was 26 percent in patients treated with medical therapy alone versus 9 percent in patients with both CEA and medical therapy. The absolute risk reduction of 17 percent with endarterectomy was thought to be so great that the study was halted prematurely as treatment efficacy had been established. Subsequently, the benefit of endarterectomy for severe stenosis was shown to be durable at eight years of follow-up.[5] The European Carotid Surgery Trial (ECST) similarly yielded a significant decrease in the incidence of stroke at three years that outweighed perioperative surgical risk in their surgical arm for severe stenosis.[6] Thus, the NASCET and ECST studies showed unequivocal evidence that CEA and medical therapy was superior to medical therapy alone for severe symptomatic carotid stenosis.

On the other end of the spectrum, mild symptomatic carotid stenosis (less than 50 percent) did not show benefit from CEA. In the parallel NASCET study that randomized patient with moderate symptomatic carotid stenosis (< 70 percent) to either CEA plus medical therapy or medical therapy alone, patients with symptomatic carotid stenosis less than 50 percent had a five-year ipsilateral stroke risk of 14.9 percent in the surgical arm and 18.7 percent in the medical arm (P = 0.16). Thus, patients with symptomatic mild carotid stenosis should generally be treated with best medical management.

The evidence is more complex for moderate symptomatic carotid stenosis (50 to 69 percent). NASCET revealed a reduced, but nonetheless significant benefit to carotid endarterectomy in patients with moderate symptomatic carotid stenosis (50 to 69 percent), with five-year ipsilateral stroke risk of 15.7 percent in patients treated surgically and 22.2 percent in patients treated medically (P = 0.045).[5] Among patients with moderate stenosis, the long-term benefits of surgery were greatest in patients with a recent stroke as opposed to transient ischemic attack, hemispheric symptoms as opposed to retinal symptoms, and male sex. In fact, there was negative benefit for patients with retinal symptoms only.

For men with moderate symptomatic stenosis, the five-year risk of ipsilateral stroke was 25 percent for medically treated patients and 17 percent for surgically treated patients. For women, however, the five-year risk of ipsilateral stroke was 15 percent for medically treated patients and 14 percent for surgically treated patients. To put things into perspective, to prevent one ipsilateral stroke during a five-year period in men, 12 patients would have to be treated with carotid endarterectomy. That number for women is 67. Population-based studies have shown that women have a lower incidence of stroke in comparison to men across almost all age groups over 55, with the exception of a slightly higher incidence of stroke in the 80 – 84 year old age group for women.[7] When data was taken from the NASCET and the ASA and Carotid Endarterectomy (ACE) Trial groups to compare the risk of endarterectomy in women versus men, contrary to men, there was no benefit to CEA in women with moderate symptomatic stenosis.[8] Furthermore, the 30-day perioperative risk of death was significantly higher in women (2.3 percent) than in men (0.8 percent).

When the NASCET group was reviewed to compare the benefits of CEA in patients of 75 years and older to those aged 65 to 74 and less than 65 years, the absolute risk reduction among patient with moderate (50 to 69 percent) symptomatic stenosis was significant only in those over 75 years.[9] Thus, when it comes to moderate symptomatic carotid stenosis, patient selection is key with meticulous clinical evaluation and exclusion of disorders that put the patient at increased risk of anesthesia or immediate cardiac complications. Good results can be achieved in this group of patients under the care of a skilled surgeon, especially for elderly men with recent hemispheric symptoms.

Perioperative risk of carotid endarterectomy

Among 1,415 patients who underwent carotid endarterectomy in the NASCET group, there were 92 perioperative outcome events (6.5 percent); 30 events were intraoperative and 62 events were postoperative.[10] However, the rate of permanently disabling stroke and death was only 2 percent. The majority was a result of thromboembolism. Risk factors included hemispheric versus retinal transient ischemic attack as the qualifying event, left-sided procedure, contralateral carotid occlusion, ipsilateral ischemic lesion on CT, and irregular or ulcerated ipsilateral plaque. Interestingly, a history of coronary artery disease with prior cardiac procedure was associated with a reduced risk of a perioperative event. The risk of wound complications was 9.3 percent, and cranial nerve injuries was 8.6 percent, although most of these were mild in severity. Intraoperative variables such as use of a shunt, monitoring or both were not associated with a significant increase or decrease of perioperative risk. Therefore, the decision to perform shunting should be based on a surgeon's personal experience.

Other medical complications not associated with the procedure itself occurred in 115 of 1,415 patients (8.1 percent) in the NASCET group within 30 days after CEA.[11] Cardiovascular complications were most common, followed by respiratory complications. Medically treated patients experienced similar complications but with one-third the frequency. Endarterectomy was approximately 1.5 times more likely to trigger these medical complications in patients with history of angina, myocardial infarctions or hypertension.

We must be careful, however, with regard to patients that have "high surgical risk." There are certain conditions that pose a high surgical risk to carotid endarterectomy, but there is an even higher risk to the patient by not performing the procedure. It is not uncommon to have carotid disease contralateral from the symptomatic side. An occluded contralateral carotid artery significantly increased the risk of stroke when associated with severe stenosis of an ipsilateral carotid artery by more than two times. Medically treated patients with severe ipsilateral stenosis and an occluded contralateral artery had a risk of stroke of 69.2 percent at two years. The risk of stroke of patients treated surgically in addition to medical management was 22.1 percent, a relative risk reduction of 68.2 percent, which favors surgery even in the setting of a high perioperative rate of stroke or death of 14.3 percent in this group of patients.

NASCET was one of the only early trials that collected baseline creatinine functions. A comparison was made among patients with Stage 3 chronic kidney disease (CKD) and those with preserved kidney function. In the severe stenosis group, medically treated patients with Stage 3 CKD were found to have a two-year ipsilateral stroke risk of 31.6 percent compared to 19.3 percent in patients with preserved kidney function.[12] Carotid endarterectomy reduced the risk of stroke by 82 and 51 percent of patients with Stage 3 CKD and preserved renal function, respectively. Thus, even though patients in the Stage 3 CKD group had a 30-day perioperative risk of myocardial infarction, congestive heart failure, or arrhythmia of 6.5 percent compared to 1.2 percent in the group with preserved renal function, the dramatic stroke risk reduction in patients who undergo CEA favors surgery in this group of patients who have severe symptomatic carotid stenosis.

Carotid stenting

Initially, pooled evidence from randomized control trials of endarterectomy versus stenting showed a higher rate of stroke or death in the stenting groups.[13] The standard of care for patient with symptomatic 70 to 99 percent stenosis remains CEA plus best medical management. Carotid artery stent placement (CAS), however, is an important alternative in patients with prior neck irradiation, prior endarterectomy, or high perioperative risk due to cardiac disease that would increase the risk of general anesthesia.[14] Smaller studies suggested that carotid artery stenting in high-risk symptomatic NASCET ineligible patients showed promising results with stenting.[15] It should be noted, however, as Leopore and colleagues state, "Ineligibility for a randomized carotid intervention trial should not be employed as a 'de novo' indication for carotid stenting." When 169 trial ineligible patients, as defined by "high risk" in the NASCET and ACAS trials, were compared to trial eligible patients, there was no significant difference in the stroke or death rate (P = 0.17).[16]

The Protected Carotid Artery Stenting versus Endarterectomy in High Risk for Endarterectomy (SAPPHIRE) randomized trial compared endarterectomy to carotid artery stenting with the use of an emboli-protection device in 334 patients with high-risk conditions for endarterectomy and with a symptomatic carotid stenosis of 50 percent or higher or asymptomatic stenosis of at least 80 percent. This study found that, for a primary end point of the cumulative incidence of a major cardiovascular event, defined as a composite of death, stroke or myocardial infarction within 30 days after the intervention or death or ipsilateral stroke between 31 days and one year, carotid stenting was not inferior to carotid endarterectomy. These findings were reported in October 2004 and, later that year, the FDA approved the first CAS system.

The Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) randomized 2,502 patients to undergo carotid endarterectomy or carotid stenting. It included symptomatic and asymptomatic patients. For symptomatic patients, the criteria were 50 percent or more on angiography, 70 percent on ultrasonography, or 70 percent or more on computed tomographic angiography (CTA) or magnetic resonance angiography (MRA) if ultrasonography was 50 – 69 percent. For asymptomatic patients, the criteria were stenosis of 60 percent or more on angiography, 70 percent or more on ultrasonography, or 80 percent or more on CTA or MRA if the stenosis on ultrasound was 50 to 69 percent. There was no significant difference between the two groups in the primary composite endpoint of stroke, myocardial infarction or death from any cause during the periprocedural period, or any ipsilateral stroke within four years (7.2 percent for CAS and 6.8 percent for CEA, P = 0.51). There was also no difference in treatment effect for symptomatic status (0.84) or sex (0.34). Periprocedural rates of myocardial infarction and stroke, however, differed in the two groups. The risk of periprocedural myocardial infraction was 1.1 percent for CAS and 2.3 percent for CEA (P = 0.03) and the risk of periprocedural stroke was 4.1 percent for CAS and 2.3 percent for CEA (P = 0.01). Although both stroke and myocardial infarction are associated with significant morbidity and mortality, quality-of-life analyses among survivors in this trial at one year showed that stroke had a greater adverse effect. CAS tended to show greater efficacy in younger patients and CEA in older patients, with a crossover at approximately 70 years old, which is likely because the periprocedural stroke risk with CAS increases as vessel tortuosity and proximal plaque burden increase with age.

It is important to note that CAS technology is continually improving. The early CAS studies without distal embolic protection had significantly higher rates of major adverse event at 30 days compared to newer studies such as SAPPHIRE. In fact, the Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Stenosis (EVA-3S) trial was stopped and had to undergo redesign when it was found that not having distal embolic protection increased the risk of stroke rate 3.9 times versus those treated

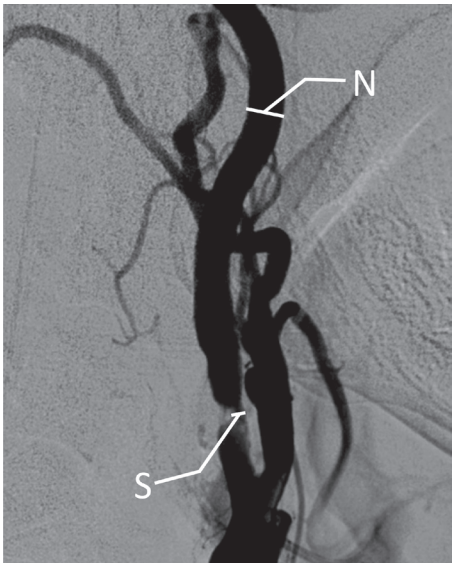

Figure 1: Lateral cervical angiogram shows the anatomical sites used in calculating percent stenosis by the North American Symptomatic Carotid Endarterectomy Trial criteria. Diameter of the vessel at the site of maximal stenosis is indicated by S, and the normal vessel diameter is indicated by N. Percent stenosis = (1 – S/N) x 100.

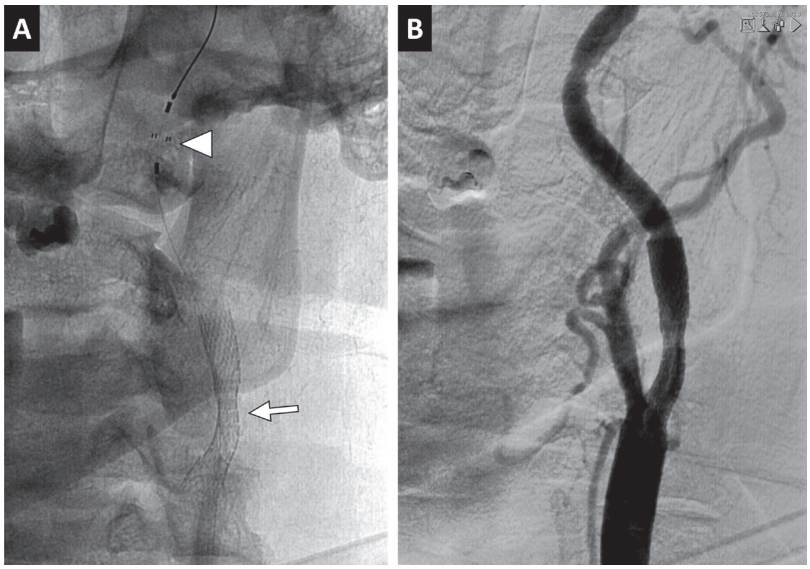

Figure 2: (A) Left anterior oblique view of cervical fluoroscopy without contrast injection shows a carotid stent (arrow) deployed such that it is centered across the area of maximal stenosis with a distal protection device (arrowhead) in place in the distal cervical left internal carotid artery. (B) A left anterior oblique common carotid angiogram shows minimal residual stenosis after stent placement in the same case presented in Figure 1.

with protection.[17] Distal embolic protection decreased postprocedural MR abnormalities from 29 to 7 percent.[18] In addition, a systematic review revealed a decrease of stroke or death risk of 1.7 percent with distal protection compared with 5.5 percent without.[19] Even with the use of distal protection devices, however, the lesion is crossed at least once in an unprotected state (Figure 2). More recently, proximal protection with flow reversal CAS systems have been developed and have shown promising initial results with 30-day stroke risk less than 2 percent in a meta-analysis of 2,397 patients.[20] This technique aims to create flow reversal from contralateral carotid and vertebrovasilar collateral intracranially, thereby flushing emboli proximally into the CCA, allowing the lesion to be crossed only in a protected state.

Asymptomatic carotid stenosis

The evidence for treatment of asymptomatic carotid stenosis is equivocal and remains controversial. In the period from 1987 to 1993, the Asymptomatic Carotid Artery Stenosis (ACAS) randomized 1,662 patients with asymptomatic carotid stenosis to either medical therapy alone or carotid endarterectomy with medical management. It included patients with arteriography indicating stenosis of at least 60 percent or ultrasonography showing a frequency or velocity greater than the instrument specific cut point with a 95 percent positive predictive value. This study showed a 47 percent relative reduction in the risk of ipsilateral stroke and perioperative death in patients undergoing carotid endarterectomy. The risk of ipsilateral stroke at five years was 11 percent without surgery and 5.1 percent with surgery (including perioperative risk of stroke or death). While it increased the number of carotid endarterectomies in the United States where at least half of carotid endarterectomies are done in asymptomatic patients, other countries did not see a significant benefit as it was estimated that 40 CEAs would have to be performed in order to prevent one stroke in five years.[21]

From 1993 to 2003, the Asymptomatic Carotid Surgery trial (ACST) enrolled 3,120 patients with mainly asymptomatic carotid stenosis of over 60 percent.[22] ACST suggested that surgery is advantageous in patients less than 75 years of age with a life expectancy of at least

three years. In addition, it was noted that this applied to patients with more than 70 percent stenosis on ultrasound (many of whom were on aspirin, antihypertensives, and lipid lowering agents). Carotid endarterectomy reduced the five-year stroke risk from 12 to 6 percent in these patients.

In a Cochrane Review published in 2008 combining ACAS, ASCST, and a VA trial encompassing a total of 5,223 patients, the authors found a surgical perioperative stroke or death risk of 2.9 percent. For the primary outcome of perioperative stroke or death or any subsequent stroke, patients undergoing carotid endarterectomy had better outcomes than patients in the medical arm. However, for any outcome of stroke or death, there was only a nonsignificant trend toward fewer events in the surgical group.[23]

In a study concentrating on risk factors for the progression and regression of risk factors in asymptomatic carotid stenosis, it was found that younger age, high grade of stenosis, absence of discrete white areas in the plaque, and taking lipid-lowering therapy were independent predictors of increased incidence of regression.[24] Independent predictors of progression included high serum creatinine, male gender, not taking lipid lowering therapy, low grades of stenosis and increased plaque area.

Thus, the management of asymptomatic patients has been subject to debate, and the identification of patients who would benefit from surgical intervention is considerably more challenging than symptomatic carotid stenosis, mainly because compared to symptomatic carotid stenosis, the risk of stroke is lower in asymptomatic disease to begin with, and the risk reduction with carotid endarterectomy is relatively modest. In addition, the risk of stroke in asymptomatic stenosis has predictably improved over the past couple decades since the landmark papers, ACAS and ACST showed benefit to carotid endarterectomy for this disease, mainly secondary to the development of more aggressive medical management such as lipid-lowering and antihypertensive medications.[25] More recent population studies have found a 10-year risk of ipsilateral stroke of 9.3 percent in patients with more than 50 percent stenosis,[26] which is substantially lower than the natural history of this disease that was represented in the classic trials, ACAS and ACST. In fact, a regression-meta analysis that reviewed 41 studies between 1978 and 2009 found that the risk of ipsilateral stroke or transient ischemic attack have declined by approximately 40 percent per decade over the past 25 years.[27] As a result, until new data support or contradict these conclusions in an evidence-based manner, the best management for most subjects with asymptomatic carotid stenosis is best medical management, including treatment of hypertension, diabetes mellitus, hyperlipidemia, smoking cessation, prophylactic ASA, and monitoring for the development of treatable cardiac conditions. It is also reasonable to develop institutional algorithms for treatment of this disease where someone with a long life expectancy and severe asymptomatic stenosis may be treated with CEA or CAS.

Surgeon experience and expertise

It is important that carotid endarterectomies are performed by experienced surgeons with an appropriate amount of surgical volume. The multiple trials on carotid endarterectomies have been highly selective in their process of surgeon selection, requiring careful audits and excluding surgeons with poor outcomes. ACAS, for example, not only denied 40 percent of applicants without excellent outcomes but also halted the participation of surgeons with poor outcomes during the trial. Thus, to obtain the only modest benefit from CEA in asymptomatic or moderate symptomatic carotid stenosis, surgeons must first have extremely low perioperative risk. Comparing surgical outcomes between ACST and ACAS highlights the importance of surgical expertise in outcomes. ACST surgeon selection was not as stringent as ACAS, selecting surgeons with an operative risk under 6 percent (stroke or death within 30 days of surgery) for their prior 50 cases. Contrary to ACAS, once in the ACST trial, surgeons were not excluded for poor outcomes. The 30-day operative risk of death in ACAS was 0.4 percent compared to 1.11 percent for ACST. The 30-day operative risk of death and stroke combined was also significantly lower in ACAS than in ACST, 1.5 and 3.1 percent, respectively. NASCET reported a perioperative risk of major stroke and death of 2.1 percent.[4] If a surgeon had a perioperative risk of 10 percent, there would be no significant benefit between medical and surgical arms in patients with severe stenosis. Therefore, when making a treatment choice, it is prudent to extrapolate those results with surgeons with an equivalent surgical acumen.

Similar supporting data have been found with the placement of carotid artery stents. The Carotid Stenting Trialists Collaboration encompasses patient data from multiple key carotid stenting studies including the Endarterectomy Versus Angioplasty in patients with Symptomatic Severe Carotid Stenosis trial (EVA-3S), the Stent Protected Angioplasty versus Carotid Endarterectomy trial (SPACE), and the Internal Carotid Stenting Study.[28] Operator pooled effect among 1,546 patients who underwent carotid stent placement was studied; 7.8 percent had a stroke or death within 30 days of the procedure. Interestingly, the 30-day stroke or death did not differ with operator lifetime experience. However, there was a significant difference in outcomes (30-day stroke or death risk) between operators with low (mean under 3.2 procedures/year, risk 10.1 percent), intermediate (mean 3.2 to 5.6 procedures/year, risk 8.4 percent) and high (over 5.6 procedures/year, risk 5.1 percent) operative volume.

Conclusion

The North American Symptomatic Carotid Endarterectomy Trial and the European Carotid Surgery Trial has unequivocally shown the benefit of CEA in patients who are symptomatic with 70 to 99 percent stenosis. It appears that there are patients with moderate stenosis of 55 to 69 percent who may benefit from the procedure. The literature suggests this group includes older patients, men and those suffering from recent hemispheric stroke. Carotid stenting is an alternative treatment to endarterectomy in carefully selected patients who may not be good surgical candidates for anatomic reasons or medical comorbidities.

Although stenting is an alternative to the gold standard procedure, CEA, the technology of stenting is continually improving. The treatment of asymptomatic stenosis remains a matter of intense debate and requires further studies as medical management has seen vast improvement since the publication of earlier research studies. In addition, the small advantage of endarterectomy for asymptomatic patients may be abolished by the incorporation of newer generation, more aggressive medical therapies. CREST2, a trial that will compare carotid endarterectomy, stenting and current best medical management will be key in further understanding the treatment of asymptomatic carotid stenosis.

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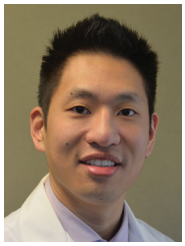
Mechanical Thrombectomy for Pediatric Stroke:
Two Illustrative Cases, Review of the Literature and Technical Recommendations

Authors



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Introduction

Pediatric ischemic strokes are relatively uncommon, with an estimated annual incidence ranging from 0.58 to 7.91 per 100,000.[1-3] The incidence of AIS in children appears to be increasing, likely secondary to an increased awareness and increased detection as imaging techniques have improved and become more widely accessible. The etiology of acute ischemic stroke (AIS) in the pediatric population differs from that of adults. Conditions most commonly associated with AIS in children include arteriopathies, cardiac disorders, infection, prothrombotic states and trauma.[4-7]

Treatment of strokes caused by arterial occlusion in adults has been well established, including the use of intravenous and intra-arterial tissue plasminogen activator (tPA).[8-11] Recent trials have also demonstrated the efficacy of endovascular mechanical thrombectomy, demonstrating significantly improved rates of functional independence and a favorable safety profile compared with IV fibrinolysis alone.[12-15] There are no clear guidelines for the management of AIS in children. The establishment of clinical trials is limited for several reasons, including the low incidence of strokes in this population.

The use of mechanical thrombectomy in pediatric strokes has been described in several case reports and small case series.[16-37] We present two illustrative cases, review the literature on pediatric thrombectomy for AIS, and discuss the unique decision-making and technical challenges associated with these procedures.

Illustrative Cases

Case 1

A 9-year-old boy was found on the floor by his parents after they heard him fall in the middle of the night. He had left-sided weakness and a left facial droop. His National Institute of Health Stroke Scale (NIHSS) was 7 on arrival. Noncontrasted CT of the head was performed, which showed a dense right middle cerebral artery (MCA) sign and no evidence of hemorrhage. He was outside the window for intravenous tPA. MRI and magnetic resonance angiography (MRA) with perfusion sequences showed a large area of diffusion-perfusion mismatch in the right MCA distribution (Figure 1) and a right M1 segment MCA occlusion.

The patient was taken to the neuroendovascular suite and intubated. A 5 French (Fr) sheath was placed in the right common femoral artery (CFA) and a 5 Fr 90 cm Envoy (Codman & Shurtleff, Inc., Raynham, MA) was navigated into the distal cervical right internal carotid artery (ICA). Right ICA injections showed a right M1 segment MCA occlusion just distal to the origin of the right anterior temporal artery (Figures 2A and 2B). Successful mechanical thrombectomy was performed with a 3 mm x 20 mm Trevo retrievable stent device (Stryker Neurovascular, Fremon, CA). Two passes with the Trevo were performed while under continuous aspiration through the base catheter during retraction of the retrievable stent. Thrombolysis in cerebral infarction (TICI) 2b right MCA recanalization was achieved at 9.5 hours from the last time the patient was known to be normal. This procedure was complicated by thromboembolic occlusion of the A2 segment of the right anterior cerebral artery (ACA) (Figures 2C and 2D).

On post-thrombectomy day one, he was extubated and his NIHSS was 4. Transesophageal echocardiogram showed severe restrictive cardiomyopathy. An implantable cardiac defibrillator (ICD) was placed in the patient, and he was listed for cardiac transplantation. He was discharged home on post-thrombectomy day nine with a NIHSS of 1 (for mild left pronator drift).

Case 2

A 17-year-old boy with Down syndrome was found slumped over on a toilet by his family. He was nonverbal, with right-sided weakness and a right facial droop. On arrival, his NIHSS was 12. MRI and MRA of the brain with perfusion weighted imaging showed a large area of diffusion-perfusion mismatch in the left MCA distribution and a distal left M1 segment MCA occlusion (Figures 3A and 3B).

Intravenous tPA was administered, and the patient was urgently taken to the endovascular suite. A 6 Fr sheath was placed in the right CFA, and a 6 Fr 90 cm Envoy catheter (Codman & Shurtleff, Inc., Raynham, MA) was placed in the distal cervical left ICA. Left ICA injections showed a distal left M1 segment MCA occlusion (Figures 3C and 3D). Successful mechanical thrombectomy was performed with a 4 mm x 20 mm Solitaire retrievable stent device (Covidien, Plymouth, MN) after a single pass, while under aspiration through the base catheter during retraction of the Solitaire device (Figure 3E). TICI 2b recanalization of the left MCA was achieved at 5.5 hours from the time of symptom onset. There was complete recanalization of the anterior division and partial recanalization of the posterior division of the left MCA; however, on post-thrombectomy left vertebral artery injections, there was good leptomeningeal collateral circulation to the posterior division of the left MCA territory from the left posterior cerebral artery (PCA) (Figures 3F to 3I).

On post-thrombectomy day one, the patient's PedNIHSS improved to 5. He was discharged home on post-thrombectomy day four. A bubble study showed a patent foramen ovale with right to left shunt, which was subsequently closed endovascularly.

Discussion

Ischemic strokes are a cause of tremendous morbidity and mortality in the pediatric population. While the mortality rate in children (3 to 6 percent) is lower than in adults, there is significant morbidity, with 70 percent of patients suffering from disabling neurologic deficits.[6,38]

Pediatric ischemic strokes have a low incidence, which often delays diagnosis. Studies have found that the time from symptom onset to diagnosis in children could be up to 25 hours.[39,40] Many of the signs and symptoms in pediatric stroke can mimic other disease processes, causing further delay. Additionally, the widely varying etiologies of pediatric ischemic infarcts pose a challenge to timely diagnosis and treatment.[4-7]

Unlike the treatment of adult ischemic strokes, there are no clear guidelines in the management of AIS in the pediatric population. While the use of tPA in adults with AIS is well established, the efficacy and safety of tPA use in children is not well understood. The American Heart Association (AHA) scientific statement does not endorse the use of thrombolytics in children, except in clinical trials.[41] The Thrombolysis in Pediatric Stroke (TIPS) trial, the first prospective trial in acute pediatric stroke, attempted to determine the efficacy of IV tPA but was closed in 2013 after low accruement.[42] Additionally, there are differences in the pharmacokinetics and dose-response for thrombolytics in this population, as the coagulation and fibrinolytic systems have not yet fully matured.[29] These factors make it difficult to establish optimal dosing of thrombolytics in children.

The treatment and management of ischemic strokes in the pediatric population create many challenges. The relatively low incidence of pediatric ischemic strokes poses a significant barrier to the development of clinical trials that evaluate the efficacy and safety of treatment modalities. Successful use of endovascular mechanical thrombectomy has been described in several case reports and small case series, but no large trials have been performed to date. A review of the literature revealed 31 reported cases,[17-37] including the two cases we presented here (Table 1). Mittal and colleagues had previously published a nontechnical case report on Case 2; the data was accounted for in

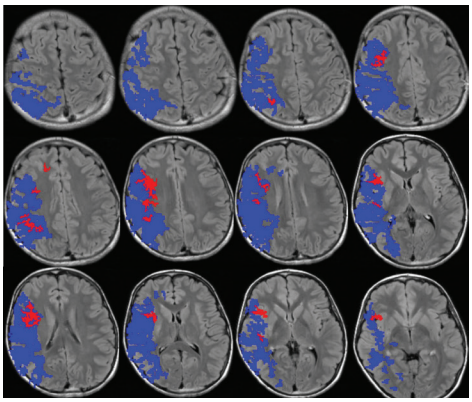

Figure 1: In Case 1, MRI with diffusion and perfusion weighted sequences processed using Olea Sphere (Olea Medical Solutions, Inc., Cambridge, MA) shows volume of core infarct in red and hypoperfusion in blue, consistent with a large area of ischemic penumbra in the right MCA distribution.

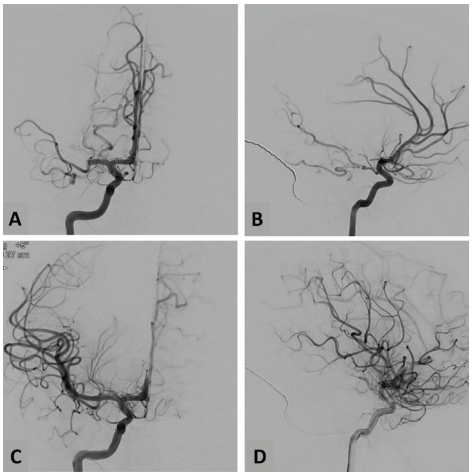

Figure 2: In Case 2, (A) digital subtraction angiography (DSA) anterioposterior (AP) and (B) lateral views show right MCA occlusion at the M1 segment just distal to the origin of the right anterior temporal artery on right ICA injections. (C) Post-thrombectomy DSA AP and (D) lateral views show recanalization of the right MCA and thromboembolic occlusion of the A2 segment of the right ACA.

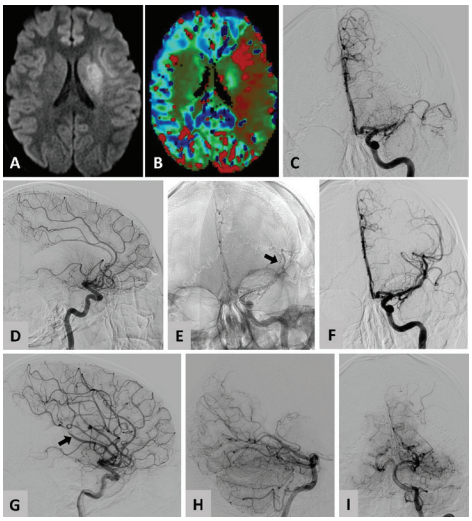

Figure 3: In Case 2, (A) MRI diffusion weighted imaging shows a relatively small area of core infarct involving the left basal ganglia and (B) a large area of hypoperfusion on time-to-peak perfusion sequences, consistent with a large area of ischemic penumbra in the left MCA distribution. (C) DSA AP and (D) lateral views show a left MCA occlusion at the M1 segment. (E) DSA AP native view with a Solitaire retrievable stent (Covidien, Plymouth, MN) deployed shows distal tines of the stent to be in the anterior division of the left MCA (arrow). (F) Post-thrombectomy DSA AP and (G) lateral views show complete recanalization of the anterior and partial recanalization of the posterior division of the left MCA. There is stagnant flow in the posterior division of the left MCA (arrow). (H) Post-thrombectomy DSA AP and (I) lateral views of left vertebral artery injections show good leptomeningeal collateral circulation provided to the posterior division of the left MCA territory via the left posterior cerebral artery.

our numbers.[35] The patient ages ranged from 2 to 17, with initial NIHSS from 2 to 36. Thrombectomy devices used were as follows: Solitaire in 12 cases (39 percent), Penumbra in nine cases (29 percent), Merci in seven cases (23 percent), Trevo in three cases (10 percent), and other devices in four cases (13 percent). In several cases, more than one thrombectomy system was used. There was a wide range of time to treatment, from 3.5 hours to 72 hours, with an average time of 13 hours. This is beyond the recommended eight-hour onset to revascularization time from the REVASCAT trial, although current studies such as the Trevo and Medical Management Versus Medical Management Alone in Wake Up and Late Presenting Strokes (DAWN) trial are investigating the efficacy and safety of mechanical thrombectomy up to 24 hours.[15] All but one reported case showed positive results,with significant improvement of neurologic deficits.[20] Intravenous tPA was used in four cases, and intra-arterial tPA was used in six cases.[18-21,25,26,29,35] Two cases used balloon angioplasty in addition to mechanical thrombectomy.[17,29]

The technical challenges of performing endovascular procedures on pediatric patients must be considered. Femoral arterial access in children is often limited to 4 Fr and 5 Fr sheaths in order to decrease the risk of morbidity related to arterial access. However, in a retrospective review of 268 pediatric endovascular procedures, Gross and colleagues had only one case of transient femoral artery associated morbidity.[43] To minimize the chance of arterial injury, they followed a general sizing guide for access catheters by Franken and colleagues.[44] However, the use of smaller sheaths limits the devices that can be used. Frequently, adult mechanical thrombectomy procedures are performed through a minimum 8 Fr sheath that enables utilization of balloon guide catheters and certain larger caliber aspiration catheters, such as the Penumbra 5 Max ACE (Penumbra Inc, Alameda, CA). Balloon guide catheters commonly employed for acute stroke interventions are 8 Fr systems or greater. These catheters have the added benefits of providing flow arrest during retraction of the retrievable stents and allowing for more effective aspiration during stent retrieval. Use of balloon guide catheters has been demonstrated to potentially decrease distal thromboembolic phenomena during endovascular mechanical thrombectomy procedures in the setting of AIS; however, due to their increased size, these catheters are typically unavailable for pediatric thrombectomy patients.[45,46]

At our Comprehensive Stroke Center, it is our practice to perform pediatric diagnostic and interventional angiograms through 4 Fr or 5 Fr arterial access. In select pediatric patients who are adult-sized, we will extend our access to 6 Fr if an intervention is necessitated. In our experience with pediatric interventional procedures, we have found that a 4 Fr Cook Shuttle Sheath (Cook Medical, Bloomington, IN) or a 5 Fr Envoy catheter provide adequate access for selective catheterization and sufficient inner diameter (ID) to allow for passage of a variety of microcatheters and devices. The 4 Fr Shuttle Sheath is a particularly versatile system that effectively offers a 5 Fr working ID (0.059 inches) with an outer diameter (OD, 0.072 inches) that is less than the OD of a 5 Fr guide sheath. Through these platforms, the full complement of currently approved retrievable stents available to centers in the United States may be used for mechanical thrombectomy procedures in the pediatric population.

Conclusion

The treatment of AIS in the pediatric patient presents a very real challenge. While there are currently no clear guidelines, the use of endovascular mechanical thrombectomy in this population may be considered for patients at centers with experienced neurovascular teams. The illustrative cases presented here emphasize the considerations and challenges of endovascular treatment for AIS in children. Improved awareness of pediatric strokes and multicenter trials to evaluate the efficacy and safety of endovascular mechanical thrombectomy in this population, along with intravenous and intra-arterial therapies, are greatly needed.

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Table 1: Summary of studies in which stroke intervention was carried out in pediatric patients.

Reference	Age, Sex	Presentation	Vessel	Device	Adjuvant Tx	Time to Tx (hr)	Outcome	Etiology, Risk Factors
Zaidat et al. (2005)	16 M	mRS 5	BA	IN-TIME	Balloon angioplasty	20	90d mRS 2	PFO
Tsivgoulis et al. (2008)	6 M	NIHSS 17	R ICA	Merci	IV tPA, IA tPA		90d NIHSS 2	MV repair, VSD closure
Grunwald et al. (2010)	16 F	NIHSS 36	BA	Penumbra	IA tPA	6	30d NIHSS 23	Unknown
	7 M	NIHSS 26	L ICA	Penumbra	ASA	3	30d NIHSS 0	CHF, cardiomegaly
	16 F	NIHSS 26	L M1	Phenox	IA tPA	3.5	30d NIHSS 0	PO contraceptive
Felker et al. (2010)	14 M	R hemiparesis, aphasia	L MCA	Merci	IA tPA, heparin gtt, warfarin	9	90d persistent aphasia, improvement in R hemiparesis	Heterozygous P20210G>A and MTHFR A1298C mutation, PAI-1 4G gene variant
Irazuzta et al. (2010)	12 M	NIHSS 16	R MCA	Merci	IA tPA, heparin gtt, ASA	6	12mo complete recovery	Unknown
Taneja et al. (2011)	14 F	R arm extensor posturing	BA	Solitaire	ASA, IA nimodipine, heparin gtt, warfarin	24	30d no deficits	Unknown
Xavier et al. (2012)	16 M	NIHSS 15	R ICA	Penumbra	ASA, clopidogrel, heparin gtt	72	Discharge mRS 3 / 90d NIHSS 1, mRS 1	Unknown
Tatum et al. (2013)	4-7	NIHSS 17	BA, R ICA	Merci, Penumbra	IA tPA	5.7 / 6.6	Discharge NIHSS 16 / 90d mRS 3	L atrial thrombus
		NIHSS 12	R M1	Merci, Penumbra		9.4	Discharge NIHSS 3 / 90d mRS 1	Stump embolus from dilated R ECA
		NIHSS 2	BA	Merci		10	Discharge NIHSS 0 / 90d mRS 0	Cardiac embolus
		NIHSS 5	BA	Merci		22.4	Discharge NIHSS 3 / 90d mRS 0	Arterial thrombus
Fink et al. (2013)	11 M	NIHSS 6	BA	Solitaire	IV tPA	4	90d slight dysarthria	Unknown
Fujimoto et al. (2013)	15 F	NIHSS 20	R M1	Penumbra	ASA	5.25	24hr NIHSS 11/ 90d NIHSS 1	R ICA dissection
Alnaami et al. (2013)	8 M	L hemiplegia, dysarthria	R MCA	Solitaire	ASA, warfarin		Post-intervention normal speech, L hemiparesis, mRS 1	Dilated cardiomyopathy

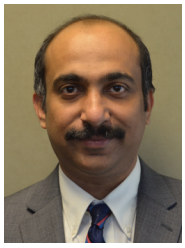
Reference	Age, Sex	Presentation	Vessel	Device	Adjuvant Tx	Time to Tx (hr)	Outcome	Etiology, Risk Factors
Dubedout et al. (2013)	7 M	NIHSS 20	BA	CAPTURE	ASA	6	Discharge NIHSS 0 / 30d mRS 0	Unknown
Hu et al. (2014)	9 F	NIHSS 16	L ICA	Penumbra	IV tPA		90d NIHSS 6	ASD
	7 M	NIHSS 17	R ICA	Solitaire, Penumbra	Balloon angioplasty		90d NIHSS 2	MV bacterial endocarditis
Sainz de la Maza et al. (2014)	12 F	NIHSS 18	R ICA, R M1	Solitaire		8	90d NIHSS 1	Unknown
Rhee et al. (2014)	9 M	NIHSS 3 / NIHSS 10	L ICA / L MCA	Solitaire	Heparin gtt, ASA, dipyridamole		24hr NIHSS 3	Dilated cardiomyopathy
Bodey et al. (2014)	10 M	NIHSS 27	BA	Revive	Heparin gtt	36	90d mRS 3	VA dissection
	5 M	NIHSS 29	BA	Solitaire	Heparin gtt	6	90d mRS 2	Gastroenteritis
	6 M	NIHSS 28	BA	Solitaire	Heparin gtt		90d mRS 0	Arteriopathy
	5 M	NIHSS 21	L MCA	Solitaire	LMWH, ASA	6	120d mRS 0	Lymphoma
Ladner et al. (2014)	5 M	NIHSS 22	BA	Solitaire	Enoxaparin, heparin gtt	9	Discharge NIHSS 1 and mRS 2 / 6w NIHSS 0 and mRS 0	VA dissection
Stidd et al. (2014)	2 M	mRS 4	R M1	Trevo	Heparin gtt, warfarin	7	30d mRS 1	Hypoplastic left heart syndrome
Mittal et al. (2015)	17 M	NIHSS 12	L M1	Solitaire	IV tPA	5.5	Discharge NIHSS 4	PFO
Vega et al. (2015)	11 M	NIHSS 16	R M1	Trevo / Penumbra		3	Discharge NIHSS 7	Atrial myxoma
Huded et al. (2015)	6 M	NIHSS 15	L VA	Solitaire	ASA, PO anticoagulation	26	Discharge NIHSS 0, mRS 0	Dissection
Wu et al. (2015)	9 M	NIHSS 7	R M1	Trevo	Enoxaparin	9.5	Discharge NIHSS 1	Restrictive cardiomyopathy
	17 M	NIHSS 12	L M1	Solitaire	IV tPA	5.5	Discharge NIHSS 4	PFO

Abbreviations

ASD: atrial septal defect, ASA: aspirin, BA: basilar artery, ECA: external carotid artery, d: day, gtt: drip, hr: hour, IA: intra-arterial, ICA: internal carotid artery, IV: intravenous, L: left, MCA: middle cerebral artery, mo: month, mRS: modified Rankin scale, MTHFR: methylenetetrahydrofolate reductase, MV: mitral valve, NIHSS: National Institute of Health Stroke Scale, PFO: patent foramen ovale, PO: by mouth, R: right, tPA: tissue plasminogen activator, Tx: treatment, VA: vertebral artery, w: week

Combined Pleomorphic Xanthoastrocytoma (PXA) and Oligodendroglioma of the Cerebellum: Case Report with Review of PXA Tumors in the Posterior Fossa

Authors



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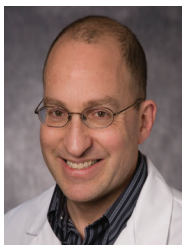

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Introduction

Cerebellar pleomorphic xanthoastrocytoma (PXA) is a rare neoplasm that is thought to originate from the subpial astrocytes.[1] PXAs most frequently occur in the cerebral hemispheres with a particular predilection for the temporal lobe. To date, there have been only 18 cases of PXA described in the cerebellum; however, only 11 of these cases described pure PXAs (Table I). The remaining literature describes so-called PXA "collision tumors," a term describing two distinct cell populations in the same tissue sample. Of these composite lesions, there are five reports of the combined PXA-ganglioglioma and one report of a combined PXA-lipidized glioblastoma multiforme.[2-6] There are two cases of supratentorial combined PXA-oligodendrogliomas.[3,7] However, there are no known descriptions of its occurrence in an infratentorial location. This case report provides the first description of an infratentorial PXA-oligodendroglioma, which presented as an incidental lesion less than 1 cm in diameter.

Case Report

History and Physical Examination: This patient is a 53-year-old, right-handed woman who presented with a three-month history of neck pain radiating to the left arm and extending to the fourth and fifth digits. She also described numbness and tingling along the same distribution. A trial of prednisolone did not completely resolve her symptoms. Her past medical history was notable for left-leg deep vein thrombosis with a resultant pulmonary embolus, hypercholesterolemia and a heart murmur. Her neurological exam revealed left upper extremity finger-to-nose ataxia, dysdiadochokinesia, and 4/5 strength in the left bicep. The aforementioned cerebellar findings were significant enough to be concerning for a possible structural lesion.

Laboratory and Imaging Studies: Laboratory studies were significant for a hemoglobin of 16.2 and hematocrit of 48.1 percent, both abnormally elevated for a female. Magnetic resonance (MR) imaging of the cervical spine revealed degenerative changes at multiple disc levels without explanation for the patient's symptoms. However, the most cephalad of the noncontrasted cervical MR images revealed a large amount of vasogenic edema on T2 and FLAIR sequences in the left cerebellar hemisphere. Dedicated MR imaging of the posterior fossa further revealed an enhancing mass in a region of edema at the transverse-sigmoid junction, measuring 9 mm in the greatest dimension (Figure 1). There was no evidence of tonsillar herniation, ventricular effacement, or other signs of mass effect in the posterior fossa. Given the imaging findings and the patient's polycythemia, the initial differential diagnosis included hemangioblastoma and metastatic renal cell carcinoma, apart from primary cerebellar tumors.

Intervention and Postoperative Course: A right-sided paramedian suboccipital craniotomy was performed followed by a curvilinear durotomy. A small corticotomy was performed to access the lesion, followed by complete excision without complication. Frameless image-guided intraoperative navigation and somatosensory evoked potentials were utilized to assist in resection of the mass. The postoperative course was uneventful; imaging showed stable vasogenic edema with no residual enhancement (Figure 2). At one-week follow-up, the patient had a mild residual headache but had complete resolution of her appendicular ataxia. Follow-up imaging at six months revealed no evidence of residual tumor or disease progression (Figure 2). There was no hydrocephalus or evidence of mass effect with interval resolution of edema.

Pathological Findings: The resected tumor specimen consisted of two irregular fragments of pinkish white, soft to rubbery tissue measuring 1.1 x 0.7 x 0.4 cm and 0.6 x 0.4 x 0.3 cm. The tumor demonstrated a nested pattern of pleomorphic glial tumor cells surrounded by proliferating microvasculature and a reticulin-rich stroma (Figure 3). This area had positive glial fibrillary acidic protein and vimentin staining. Oil red staining demonstrated minimal lipid within the tumor. Staining for cytokeratin, CD10, inhibin, and TTF-1 were all negative. Mitotic figures were inconspicuous, and there was no visible necrosis. Preliminary pathological examination suggested a diagnosis of pleomorphic xanthoastrocytoma (World Health Organization [WHO] Grade II) with focal oligodendroglioma-like differentiation, likely representing a more aggressive component of the lesion. Genetic analysis showed no p53 mutations with intact 1pq19. Staining for inhibin and synaptophysin were both negative.

Discussion

Background

Pleomorphic xanthoastrocytomas were originally described by Kepes in 1979,[1] with more than 600 cases reported thus far. In 1991, Kros and colleagues described a PXA combined with a ganglioglioma, a finding that would later be termed a collision tumor.[8] The next year, Lindboe described the third PXA-ganglioglioma, which was

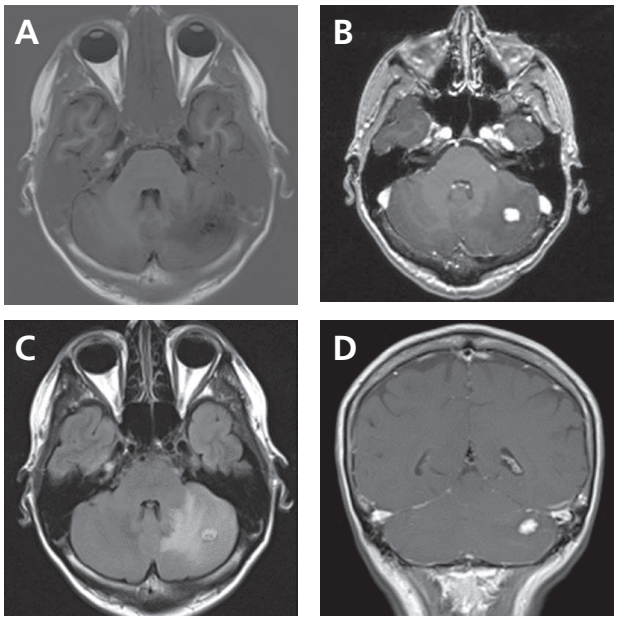

Figure 1: Preoperative MRI. (A) Axial T1-weighted image shows a hypointense lesion involving the left cerebellar hemisphere. (B) After gadolinium infusion, strong enhancement is seen sharply demarcated by the tumor's borders. (C) Axial fluid-attenuated inversion recovery (FLAIR) imaging shows a significant amount of vasogenic edema limited to the left hemisphere. (D) Coronal T1-weighted image after gadolinium infusion demonstrates cranial-caudal extent of the lesion.

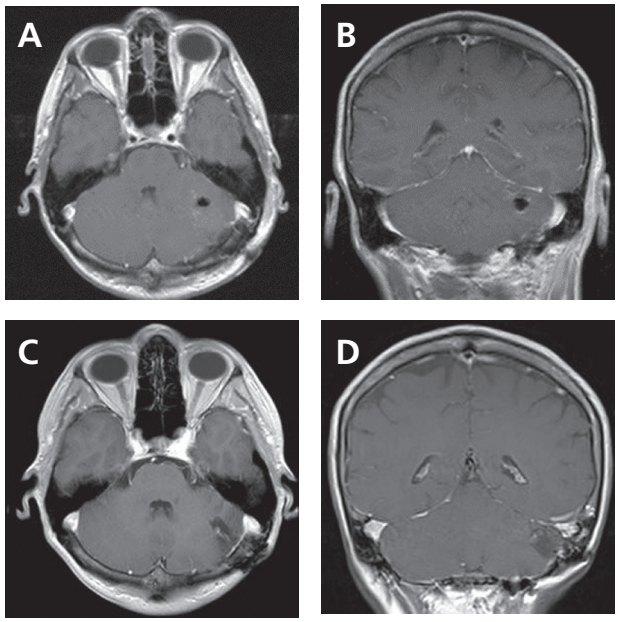

Figure 2: Postoperative MRI at 24 hours after resection. (A) Axial T1-weighted image with gadolinium contrast demonstrates complete tumor resection without residual enhancement in the resection cavity. (B) Coronal T1-weighted image with gadolinium contrast demonstrates cranial-caudal borders of resection cavity without residual enhancement. (C) Axial and (D) coronal T1-weighted images with gadolinium at six-month postoperative follow-up, showing no evidence of recurrent disease.

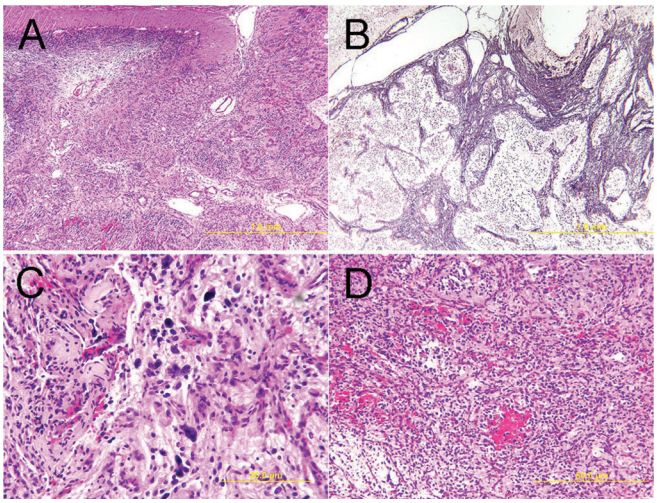

Figure 3: (A) The tumor is well demarcated from the adjacent cerebellar cortex (H&E x 40) and (B) produces a dense reticulin-rich stroma (Reticulin x 40). (C) Most of the tumor is composed of nests of tumor that include markedly pleomorphic astrocytes (H&E x 200). (D) Focally, the tumor demonstrates oligodendroglial differentiation (H&E x 100).

notable for being the first description of an infratentorial PXA.[9] Since then, there have only been fifteen reports of composite PXAs, with only five of these in the posterior fossa. A summary of case reports describing PXA collision tumors are shown in Table I. A similar summary of posterior fossa pure PXAs are shown in Table II.

Pleomorphic xanthoastrocytomas are classified as WHO Grade II astrocytic tumors.[10] They were originally thought to arise from subpial astrocytes. However, some genetic features and the relatively high occurrence of gangliogliomatous components have led some to question classification of PXAs as astrocytic in origin.

Clinical Characteristics, Natural History, and Treatment of PXAs in the Posterior Fossa

A review of available literature reveals 18 cases of posterior fossa PXAs, all of which underwent surgical excision. The mean age at diagnosis was 32 years with 12 female patients and six male patients. The average age of diagnosis in men was 38 years compared with 29 years in women. While intriguing, this difference was not statistically significant due to the small number of case reports available.

The largest PXA series to date was comprised of 98 percent supratentorial tumors and provides an excellent data set to compare and contrast the natural history of supratentorial and infratentorial PXAs.[11] Infratentorial PXAs are diagnosed, on average, six years later. Supratentorial PXAs are most often diagnosed in the setting of new onset or medication-refractory epilepsy (71 percent of cases). Not surprisingly, patients with infratentorial PXAs instead show cerebellar and cranial nerve findings and have a higher frequency of developing increased intracranial pressure. The mild delay in presentation is possibly explained by the additional progression to cause symptomatic mass effect in infratentorial PXAs. This explanation also has implications for the difference in natural history between the two lesions.

The same series provides good data regarding the mortality of PXAs. In their series, overall survival at five years was 81 percent and at 10 years was 70 percent. The statistically significant prognostic factors for decreased survival were increased or atypical mitoses and the presence of necrosis. The surgeon's estimate of total resection was the best predictor for recurrence-free survival; however, the mitotic index was still the best predictor of overall patient survival. Patients with aggressive disease typically experienced occurrence within one year and died within two years. Due to the commonly short duration of follow-up in individual case reports, this data set provides much more convincing data for extrapolating the overall survival of infratentorial PXAs.

Recurrence rates in infratentorial pure PXAs are significantly greater in comparison with their supratentorial counterparts. As shown in Table II, follow-up information is known only for 10 of the 13 cases. Even when assuming these cases to be recurrence-free, six of the 13 cases reported recurrence (46 percent), more than double the rate in supratentorial tumors (17 percent).[11] Many of these cases have immediate postoperative imaging showing enhancement in the tumor cavity. Considering the increased surgical difficulty in resecting these posterior fossa lesions, it is quite possible that this increased recurrence rate simply reflects a higher rate of subtotal resections.

Some have reported that the presence of anaplastic features in supratentorial PXAs portends a worse prognosis.[11] Review of the infratentorial cases shows recurrence in three of six cases with typical histology (that included follow-up data). There are four cases of infratentorial PXAs with anaplastic features, with three exhibiting recurrence. Although tempting to suggest that infratentorial PXAs are similar in this regard to their supratentorial counterparts, it must be noted that the only two deaths in this series were attributed to tumors without anaplastic features.

Unfortunately, only a small amount of data exists at this time to confidently guide treatment of recurrent disease. In the six cases of infratentorial PXAs with recurrence, adjuvant radiation therapy was used in four cases with additional chemotherapy in two of those cases. This small data set is further complicated by the likelihood of physicians prescribing adjuvant therapy in what they view to be more aggressive disease. Similarly, there are unfortunately no known evidence-based guidelines for treatment of recurrent supratentorial PXAs.

Infratentorial PXAs are also unique in their propensity to occur as collision tumors. In the literature describing hundreds of supratentorial PXAs, only 17 reports are of supratentorial PXA collision tumors. Conversely, in the 18 described infratentorial PXAs, five are collision tumors (28 percent). As discussed below, this difference is important when considering the natural history of a posterior fossa PXA.

Radiologic Features and Differential Diagnosis

PXAs are most often solid masses that homogenously enhance with contrast administration.[11,12] They most commonly occur in the temporal lobe (49 percent). Outside

the temporal lobe, their frequency is directly related to lobar volume and occurs (in decreasing frequency) in the frontal, parietal and occipital lobes. PXAs have a cystic component with a mural nodule in 70 percent of cases, with the remainder appearing as a solid mass with or without cystic changes. Although patients are frequently symptomatic, our case illustrates that these tumors are found incidentally. A recent case series found that 8 percent of PXAs were found incidentally during imaging for an unrelated indication.[12]

The differential diagnosis of a cystic lesion with a mural nodule includes ganglioglioma, hemangioblastoma and pleomorphic xanthoastrocytoma.[8] In a younger patient, one must also consider pilocytic astrocytoma. In the setting of anaplastic features, this differential further broadens to include glioblastoma and malignant fibrous histiocytoma. In the case discussed here, a routine screening complete blood count revealed polycythemia in our patient, placing hemangioblastoma at the top of our preoperative differential diagnosis.

Natural History of Collision PXAs

A review of the literature revealed 22 collision tumors (Table I). For simplicity, all descriptive statistics include the current case report. The demographics of these are extremely similar to those of infratentorial pure PXAs: average age at diagnosis 29.6, 55 percent male, and most commonly presenting with symptoms of mass effect.

The majority (77 percent) of these tumors were supratentorial, most often in the temporal lobe (70 percent). However, as stated, collision tumors are much more frequently found infratentorially than their histologically pure counterparts.

The vast majority of these tumors are PXA-gangliogliomas (81 percent), followed by PXA-oligodendrogliomas (17 percent), with a single reported case of PXA-DNET.[13] The second cell type appears to be important for prognostic information. PXA-gangliogliomas historically have had a recurrence rate of 20 percent, extremely similar to that of pure PXAs. However, all three previous cases of other cell types have experienced recurrence. Only one death occurred with PXA-gangliogliomas, which was ascribed to intratumoral hemorrhage. In contrast, death occurred in one of the two previously reported PXA-oligodendrogliomas and in the single case of PXA-DNET. As discussed below, it should be noted that the cause of death in the PXA-oligodendroglioma was due to subsequent development of aggressively metastatic rhabdoid meningiomas.

Similar to the discussion of adjuvant treatment in infratentorial pure PXAs, it is difficult to make firm recommendations regarding treatment of recurrent disease. In recurrent collision tumors, radiation therapy was used in four of the five patients. In contrast to pure PXAs, adjuvant radiation therapy was used following initial resection in four patients with collision tumors. Adjuvant chemotherapy was used in three cases. Two of these had anaplastic features and, despite both radiation therapy and chemotherapy, resulted in death. The third case used chemotherapy after the first recurrence and reported no further recurrences at 18 months of follow-up. For pure PXAs, many consider chemotherapy ineffective with little data to support its use.

The unsatisfactory response to adjuvant therapy and the tendency for PXAs to dedifferentiate underlines the importance of attaining a gross total resection whenever possible. In pure PXAs, extent of resection is the best predictive factor for recurrence-free survival.[11] It has been shown previously that there is a significant survival benefit in pure PXAs following gross total resection with secondary resections as required.[14]

Oligodendroglioma-PXAs in Neurosurgical Literature

This case report describes the first known description of a combined PXA-oligodendroglioma in the posterior fossa. Two previous reports of this tumor in a supratentorial location exist. The first was an 18-year-old woman who presented with progressive headache and visual disturbances.[3] Imaging revealed a superficial 4-cm lesion in the left parietooccipital region, heavily calcified with focal enhancement. Following a craniotomy for resection of the lesion, residual tumor was likely seen on imaging. This small enhancing nodule progressed and was treated with external beam radiation therapy. Follow-up at 2.8 years showed no further progression.

The second patient with a PXA-oligodendroglioma was a 25-year-old woman presenting with worsening headaches that progressed to nausea and vomiting.[7] Imaging revealed a heterogenous left temporal mass measuring 4.5 x 3.8 x 3.2 cm and causing 6 mm of midline shift. She underwent a left frontotemporal craniotomy with presumed gross total resection. However, similar to the aforementioned illustrated case, postoperative imaging revealed residual enhancement in the surgical bed consistent with residual tumor. Due to an inaccurate diagnosis of glioblastoma multiforme on intraoperative frozen section, Gliadel® wafers (Eisai Inc., Woodcliff Lake, NJ) were implanted. Postoperative review of pathology resulted in a diagnosis of PXA-oligodendroglioma; thereafter, temozolomide and external beam radiation therapy was used. The patient experienced local tumor recurrence at seven months and underwent a second craniotomy followed by procarbazine-lomustine-vincristine systemic chemotherapy. At 13 months postoperatively, follow-up imaging showed possible progression and a third craniotomy was performed, but the pathologic findings only consisted of radiation necrosis.

At 21 months postoperatively, there was no residual tumor in the left temporal lobe. However, there was a dural-based lesion overlying the left temporal lobe. Over the ensuing months, the patient developed multiple dural-based lesions consistent with rhabdoid meningiomas. She eventually died 40 months after her first resection due to metastatic spread to the spine, ribs, scalp and soft tissues of the neck.

The results of these two prior cases likely illustrate the importance of true gross total resection in the treatment of these lesions. In our case, postoperative imaging revealed no residual disease and follow-up imaging at six months similarly showed no recurrence. While data are limited, it is possible that residual disease can be controlled with radiation therapy in the short term, although the clinical outcome in the more recent of these two cases is concerning.

Classically, no genetic syndromes are associated with the development of PXAs or collision tumors; however, there are nine reports of PXAs in the setting of neurofibromatosis-1 (NF-1).[15] This possible association with NF-1 is clinically important, as these patients are more susceptible to the development of secondary tumors following radiation therapy. In a recurrent tumor resistant to a combination of

interstitial brachytherapy, external beam radiotherapy, and chemotherapy, gross total resection likely resulted in control of the primary lesion. Although not always technically possible, it is our recommendation that every attempt should be made to attain a gross total resection.

Conclusion

This report is the first known description of an infratentorial combined PXA-oligodendroglioma, found incidentally while it measured less than 1 cm. Genetic analysis revealed intact p53 as well as intact 1p19q. A review of the literature suggests that collision tumors containing a gangliogliomatous component might behave similarly to pure PXAs. However, PXAs containing non-neuronal components appear to portend a worse prognosis. Similar to pure PXAs, complete resection of collision tumors is likely the key to preventing recurrence. The role of adjuvant therapies in collision tumors is still unclear, but an increasing amount of data suggests that chemotherapy is not an effective adjuvant treatment. While the potential for recurrence and malignant progression exists, meticulous resection provides an opportunity for surgical cure of collision tumors.

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Table 1: Summary data of known cases of PXA collision tumors.

Author	Year	Age	Sex	Type	Location	Recurrence	Adj Tx	Latest f/u
Kros[8]	1991	9	F	PXA-GG	Temporal	None	None	NR @ 4 y
Furuta[16]	1992	16	M	PXA-GG	L temporal	None	RTx1	NR @ 2 y
Rao[17]	1995	19	M	PXA-GG	L temporoparietal	None	None	
Kordek[18]	1995	24	F	PXA-GG	L temporal	None	RTx1	NR @ 4 y
Lach[19]	1996	23	M	PXA-GG	R temporal	None	None	NR @ 12 y
Lach[19]	1996	47	M	PXA-GG	L temporal	None	None	NR @ 5 mo
Lach[19]	1996	52	F	PXA-GG	R temporal	None	None	NR @ 18 mo
Powell[20]	1996	14	F	PXA-GG	R cerebellum	Unknown	None	Unknown
Vajtai[4]	1997	32	M	PXA-GG	L temporal	None	None	NR @ 12 y
Perry[10]	1999	24	F	PXA-GG	Midline cerebellum	None	None	NR @ 7 mo
Perry[10]	1997	22	M	PXA-GG	R temporoparietal	3 over 4 y	Chemo + RT	Death @ 4 y*
Perry[10]	1997	82	M	PXA-GG	L frontal	Unknown	Unknown	Lost to f/u
Perry[10]	1997	14	F	PXA-GG	R cerebellar hemisphere	1 y	RT + chemo	NR @ 28 mo
Hessler[21]	1999	27	M	PXA-GG	R frontal	None	None	
Evans[2]	2000	60	M	PXA-GG	Midline cerebellum	None	RTx1	NR @ 16 mo
Perry[10]	2001	18	F	PXA-oligo	L parietooccipital	None	RTx1	NR @ 2.8 y
Ebato[22]	2002	9	F	PXA-GG	R frontal	14 mo	None	
Yeh[5]	2003	12	M	PXA-GG	Suprasellar	None	None	Unknown
Ishizawa[13]	2007	60	M	PXA-DNET	Temporal lobe	1	RT x1	Death @ 8 mo
Sugita[23]	2009	13	M	PXA-GG	L temporal lobe	None	None	NR @ 7 mo
Hattab[7]	2011	25	F	PXA-oligo	L temporal lobe	6 mo	Chemo + RT	Death from rhabdoid meningioma
Manjila (present case)	2011	53	F	PXA-oligo	R cerebellar hemisphere	None	None	NR @ 6 mo

*With each resection of this patient's tumor, the malignant component progressed in prominence and dysplasia. The majority of the fourth resection exhibited pseudopalisading and necrosis, consistent with glioblastoma multiforme. The suspected cause of death was intratumoral hemorrhage.

Abbreviations

Adj: adjuvant
Chemo: chemotherapy
F: female
f/u: follow up
L: left
M: male
mo: month
NR: no recurrence
PXA-GG: Pleomorphic xanthoastrocytoma-ganglioglioma collision tumor
PXA-Oligo: Pleomorphic xanthoastrocytoma-oligodendroglioma collision tumor
PXA-DNET: Pleomorphic xanthoastrocytoma-dysembroplastic neuroepithelial collision tumor
R: right
RT: radiation therapy
Tx: treatment
y: year

Table 2: Summary of known cases of infratentorial PXA.

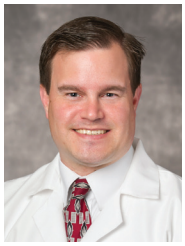
Author	Year	Age	Sex	Type	Location	Recurrence	Adj Tx	Latest f/u
Lindboe9	1992	27	M	Anaplastic	Midline cerebellar	12 y	None	NR 11 mo
Glasser24	1995	36	F	Anaplastic	R frontal	3 y, 5 y, 16 y	RTx1	None
Lim25	1997	3 mo	F	Pure	Midline cerebellum	None	None	NR@ 13 mo
Rosemberg26	2000	68	M	Pure	Midline cerebellum	Unknown	Unknown	Unknown
Kumar6	2003	15	M	Pure	R cerebellar hemisphere	Unknown	None	Unknown
Gil-Gouveia27	2004	40	M	Anaplastic	CPA	27 mo	None	Unknown
Naidich28	2004	51	F	Pure	Midline cerebellum	2 mo	RT	Unknown
Saikali29	2005	36	F	Pure	R occipital and R cerebellar hemisphere	6 mo	RT + chemo	Death @ 36 mo
Chang30	2006	4	F	Anaplastic	Midline cerebellum	None	RT + chemo	NR @ 12 y
Kurschel31	2006	6	F	Pure	CPA	None	None	NR @ 3 y
Hamlat32	2007	58	F	Pure	L cerebellar hemisphere	3 mo	RT + chemo	Death @ 11 mo

Abbreviations

Adj: adjuvant
chemo: chemotherapy
CPA: cerebellopontine angle
F: female
f/u: follow up
L: left
M: male
mo: month
NR: no recurrence
R: right
RT: radiation therapy
Tx: treatment
y: year

The Unstudied side of Creutzfeldt-Jakob Disease

Author



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Introduction

Creutzfeldt-Jakob disease (CJD) is a human prion disease with an annual incidence of approximately one per million people per year.[1] CJD is characterized by rapid neurodegeneration with most patients surviving less than one year. A definite diagnosis of CJD is only possible with neuropathological examination, and antemortem diagnosis is purely clinical, albeit fairly reliable with the use of cerebrospinal fluid tests, electroencephalogram, and brain MRI.[2] There is no current treatment for CJD, and it is invariably fatal. The majority of cases are of sporadic etiology, but 10 to 15 percent are caused by one of several disease-causing mutations of the prion protein gene that are often autosomal dominant and highly penetrant. Despite the multiple effects the illness has on families, no one has systematically studied the caregivers of CJD patients. Since the caregivers are often the patients as well, we sought to systematically evaluate caregiver burden in CJD compared to other forms of dementia. We hypothesized that behavioral variant frontotemporal dementia and sporadic CJD would exhibit the highest caregiver burden and that the former would be largely due to prominent neuropsychiatric symptoms, whereas the later would be mediated by neurological symptoms and rapid progression.

Study design

The study was performed with data previously collected from the Johns Hopkins Frontotemporal Dementia and Young-Onset Dementia Clinic between May 2004 and February 2010. Researchers from Duke University (Alice Uflacker) and Johns Hopkins (Chiadi Onyike) assisted with study design and data analyses. A total of 223 cases of atypical dementia were seen in the clinic during this time period. For the purpose of analyses, only subjects with diagnoses of sporadic

CJD (sCJD), behavioral variant frontotemporal dementia (bvFTD), language variants of frontotemporal dementia, and young-onset Alzheimer disease were included in the study. Subjects were administered several structured scales including the Zarit Burden Interview (ZBI), Neuropsychiatric Inventory-Q (NPI-Q), the Modified Mini-Mental State Examination, Clinical Dementia Rating Scale, Geriatric Depression Scale, Katz activities of daily living scale, and Lawton-Brody scale to assess independent activities of daily living, and the Uniform Parkinson's Disease Rating Scale (UPDRS).

Results

Caregiver burden as measured by mean ZBI score differed between diagnostic groups with the highest scores occurring in caregivers of bvFTD and sCJD subjects (35 and 31 respectively, p = 0.026) (Figure 1). As expected, sCJD cases had the shortest mean survival time, but it did not account for differences in mean ZBI scores on Cox regression analyses. There were no significant differences in cognitive test scores, clinical dementia rating scales, impairments in activities of daily living and independent activities of daily living, or UPDRS scores between diagnostic groups.

A differentiating characteristic between diagnostic groups was the presence and severity of neuropsychiatric symptoms. The bvFTD and sCJD groups had the highest mean number of endorsed neuropsychiatric symptom domains on the NPI-Q (5.8 and 5.5 respectively, p = 0.012) (Figure 2). Apathy and disinhibition were more likely to occur in bvFTD subjects. bvFTD and sCJD also had significantly higher NPI-Q total severity scores (11.9 and 9.9 respective, p = 0.004) and NPI-Q Caregiver Distress scores (16 and 13 respectively, p = 0.002). When examining mean ZBI scores via a Cox regression analysis, there was an interactive effect between disease category and NPI-Q total severity score (sCJD: OR = 1, p = 0.027; bvFTD: OR = 0.942, 95% CI 0.906-0.98, p = 0.003) suggesting that a combination of disease etiology and neuropsychiatric symptoms contributed to elevated caregiver burden.

Discussion

Caregiver burden is a common research topic in Alzheimer disease; however, it has been less studied in atypical dementias. Caregiving for a loved one with dementia is associated with greater overall burden as well as physical and mental health complications compared to caring for a loved one without dementia.[3] The type of dementia one has also influences caregiver burden. Atypical dementias such as frontotemporal dementia, dementia with Lewy bodies, and Parkinson disease dementia are associated with greater caregiver burden compared to Alzheimer disease.[4,5] The elevated caregiver burden observed in bvFTD in one study was attributed to increased neuropsychiatric symptoms, as cognitive and functional status of frontotemporal dementia patients did not differ from those with Alzheimer disease. Similarly, our study demonstrated elevated caregiver burden in bvFTD and sCJD compared to other types of dementia. Cognitive and functional differences between dementia types did not account for differences in caregiver burden. Similar to bvFTD, elevated caregiver burden in sCJD was attributed to greater number of endorsed symptoms, severity, and caregiver distress of neuropsychiatric symptoms. We were surprised by these findings, but perhaps we should not have been given what is known about neuropsychiatric symptoms in sCJD.

sCJD is not often thought of in terms of neuropsychiatric symptoms, but they are quite common. Aside from dementia, none of the diagnostic symptom criteria involve neuropsychiatric symptoms.[2] However, neuropsychiatric symptoms are a common feature of sCJD.[6,7] Neuropsychiatric presentations are especially common in young sCJD patients.[6,8] In a meta-analytic review, 27.5% of sCJD cases younger than 50 years of age presented with mood symptoms.[6] In fact, an initial presentation of mood symptoms in sCJD predicts younger age at disease onset, longer illness duration, and delayed time to clinical presentation.[9] Other common neuropsychiatric symptoms in sCJD include behavior or personality changes, sleep disorders, agitation, and psychosis. Visual hallucinations can also be a feature of a clinical variant of sCJD called Heidenhain variant that initially affects the posterior cortex and often has a more rapid progression.[10]

Conclusion

sCJD is associated with elevated caregiver burden compared to Alzheimer disease, similar to bvFTD. Although sCJD is associated with rapid progression and prominent neurological and psychiatric symptoms, it appears that psychiatric symptoms are the most troubling to caregivers. sCJD is invariably fatal, and there are no current treatments to slow its course or improve symptoms; however, we can treat psychiatric symptoms and help to alleviate caregiver burden.

Clinicians should strongly consider caregivers when evaluating patients with sCJD, and appropriate support should be offered. The CJD Foundation is an advocacy group dedicated to families affected by all forms of prion disease. It offers several services including educational material, advocacy, and support groups. The first-ever support group for prion disease in the United States was started by University Hospitals Case Medical Center in conjunction with the CJD Foundation and the Cleveland Area Chapter of the Alzheimer's Association. Other local support groups and even teleconference support groups are offered to families through the CJD Foundation. Assistance with diagnosis through CSF analyses, a Brain MRI Consultation Program, and CDC-funded Autopsy Program are also offered through the National Prion Disease Pathology Surveillance Center at Case Western Reserve University.

Results from this study were presented at Prion 2015 and the 2015 Annual Meeting of the American Association of Geriatric Psychiatry.

Brian Appleby, MD, reports no financial relationships with commercial interests relevant to the content of this article.

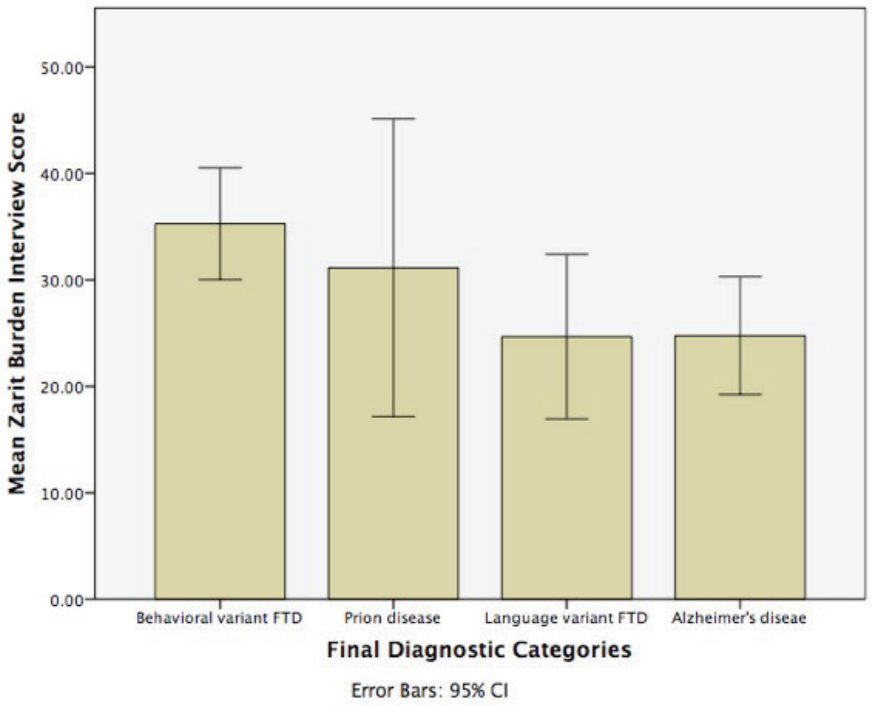

Figure 1: Mean Zarit Burden Interview scores by diagnosis (ANOVA, F = 3.29, p = 0.026). FTD = frontotemporal dementia, CI = confidence interval

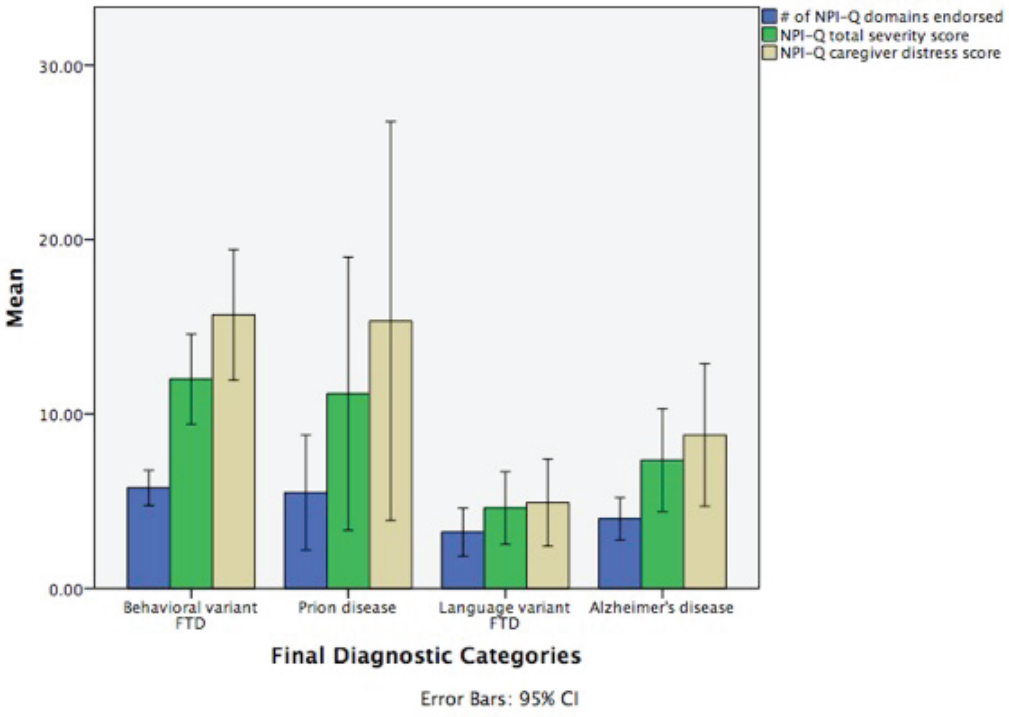

Figure 2: Characteristics of NPI-Q scores by diagnosis. Diagnostic categories differed by number of endorsed symptom domains (ANOVA, F = 3.95, p = 0.012), mean total severity scores (ANOVA, F = 4.86, p = 0.004), and mean caregiver distress scores (Kruskal-Wallis, 15.2, p = 0.002). FTD = frontotemporal dementia, CI = confidence interval, NPI-Q = Neuropsychiatric Inventory-Q

Resources

CJD Foundation: www.cjdfoundation.org

National Prion Disease Pathology Surveillance Center: www.cjdsurveillance.com

Alzheimer's Association: www.alz.org

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