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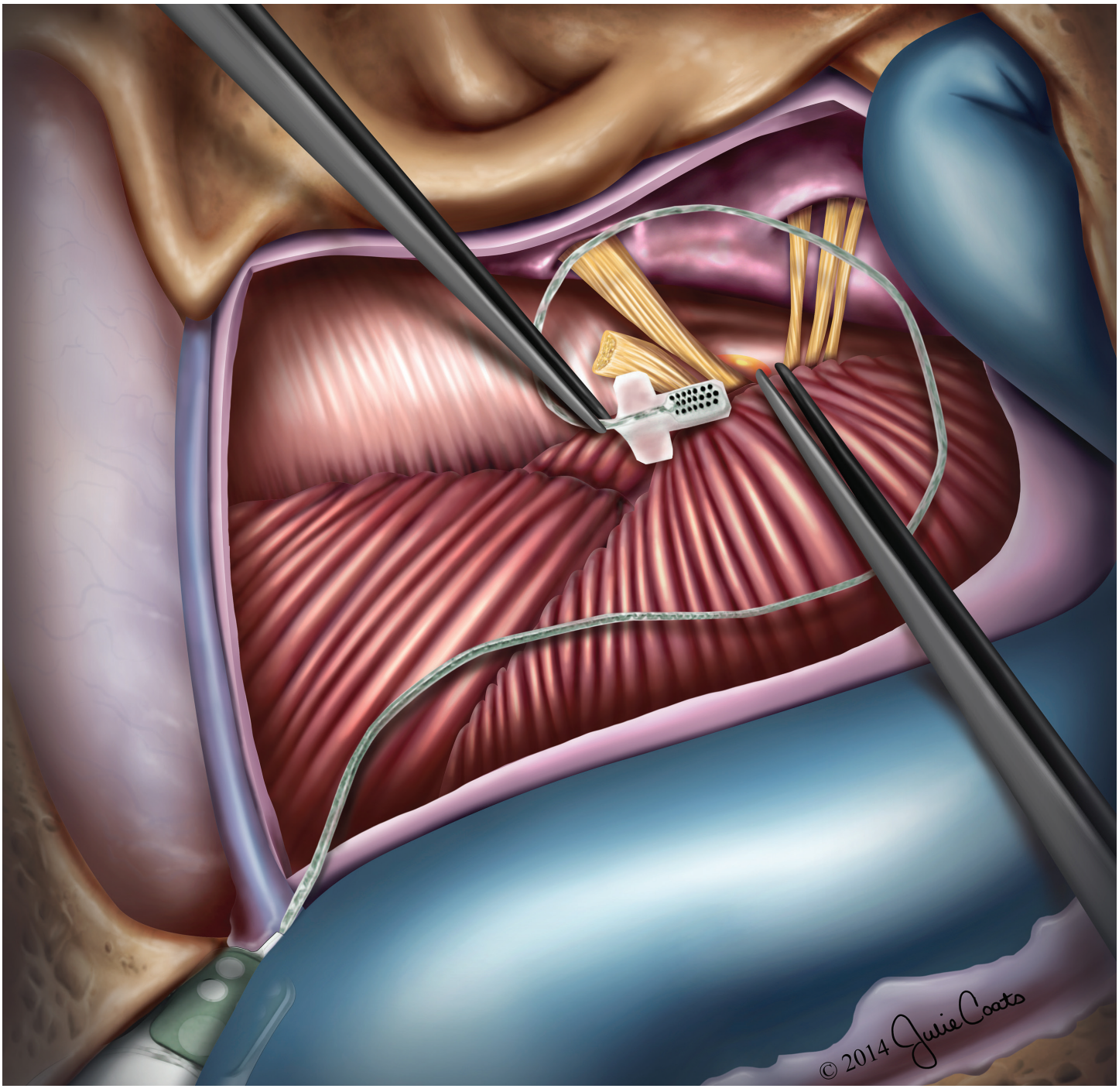

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UH Neurological Institute Journal

FROM THE EDITOR

Dear Colleague,

I am pleased to bring you the Summer 2014 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*™.

Starting off our Summer issue, Cameron Wick, MD, and colleagues discuss auditory brain implantation, a procedure first successfully conducted in Northeast Ohio at University Hospitals Case Medical Center this March. The authors review the indications and surgical technique for this innovative procedure and highlight future directions of research for the treatment of sensorineural hearing loss.

Jonathan Pace, MD, and colleagues evaluate the current treatment options for large and giant intracranial aneurysms with a thorough review of recent studies involving flow-diverting stents. In their article, the authors share their initial experience of these aneurysms and openly discuss their experience with learning to use the technology.

Next, Matthew Eccher, MD, and colleagues examine neurophysiologic intraoperative monitoring as it is used in spinal surgery. With no existing standard of care regarding such monitoring, the authors clarify current patterns of practice among neurosurgeons who perform spine surgeries and bring to light several guidelines that exist that may result in improved patient outcomes.

Wrapping up this issue, Barry Hoffer, MD, PhD, and colleagues discuss the effects of maternally transmitted mtDNA mutators. The authors report that the mutations reduce fertility, aggravate aging, and shorten lifespan, based on animal studies, and that the future of treatment may involve mitochondrial gene therapy.

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

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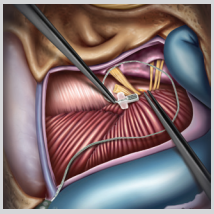

On the cover: *Auditory brain implantation. Read more about this topic in the article by Cameron Wick, MD, on page 4. (Illustration by Julie Coats.)*

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Auditory Brainstem Implantation:
Restoring Auditory Function Beyond the Cochlea

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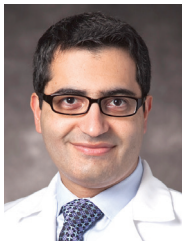

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Introduction

On March 11, 2014, the first auditory brainstem implant (ABI) in Northeast Ohio was successfully placed at University Hospitals Case Medical Center. The procedure marked a collaborative effort between the Departments of Neurological Surgery, Otolaryngology – Head and Neck Surgery, and Electrophysiologic Monitoring.

The patient, a 42-year-old female, was afflicted with neurofibromatosis type 2 (NF2) and the disease's hallmark of bilateral vestibular schwannomas. Despite attempts to control tumor growth with stereotactic radiation (CyberKnife®), surgery, and chemotherapy (bevacizumab), she ultimately developed bilateral profound sensorineural hearing loss (SNHL). A salvage attempt to stimulate the remaining cochlear nerve fibers with a cochlear implant was unsuccessful, thus making an ABI her only option for hearing restoration.[1,2] This article is a review of the indications and surgical technique for this innovative procedure and highlights future directions of research for the treatment of SNHL.

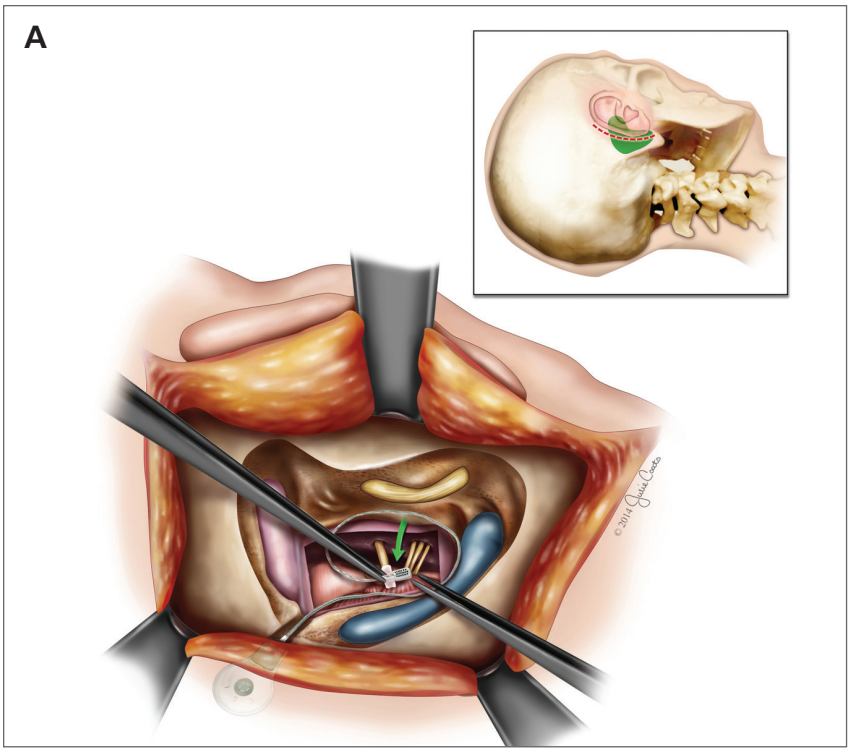
Implant Development and Indications

Drs. William House and William Hitselberger, pioneers of neurotologic surgery and advocates of the multidisciplinary approach, are credited with using the first ABI to successfully stimulate the cochlear nucleus and restore rudimentary auditory function.[3,4] The single-channel ABI they implanted in 1979 has since undergone many modifications, and all current ABI manufacturers produce multichannel devices.[5] Only Cochlear Corporation's Nucleus 24 Auditory Brainstem Implant System with a 21-channel electrode has the approval of the United States Food and Drug Administration (FDA), although devices from Med El Corporation and Advanced Bionics have been used throughout the world *(Figure 1)*.

ABI technology borrows heavily from cochlear implants. Like cochlear implants, an external processor and microphone are necessary to capture sound. The mechanical energy of sound is converted to electrical impulses that pass transcutaneously to a receiver/stimulator implanted in the skull. The electrical impulses are then sent through a wire that terminates with surface electrodes implanted adjacent to the cochlear nucleus. From the cochlear nucleus, the normal central auditory pathways transmit the signal to the auditory cortex.[6]

The necessity for an ABI arises when bilateral profound SNHL is accompanied by nonviable cochlear nerves. The cochlear nerve is the target for cochlear implants; therefore, when the nerve is absent or not functioning, it renders cochlear implants unserviceable. The most common indication is for patients with NF2, whose cochlear nerves have been irrevocably damaged by bilateral vestibular schwannomas or the treatments aimed at controlling tumor growth. An estimated 90% of NF2 patients are affected by bilateral vestibular schwannomas.[7] In 2000, the FDA granted approval for the Cochlear Corporation's Nucleus 24 ABI System in the setting of NF2 with bilateral cochlear nerve tumors, age greater than 12 years, language competency, and realistic expectations. Since then, a growing body of evidence for off-labeled uses, particularly from the European literature, supports ABI use in patients with cochlear nerve hypoplasia/aplasia, cochlear ossification, bilateral skull base trauma, other neoplastic syndromes such as von Hippel-Lindau disease, and sporadic vestibular schwannomas in patients with only one hearing ear.[8-12]

Figure 1: Photograph of the auditory brainstem implant



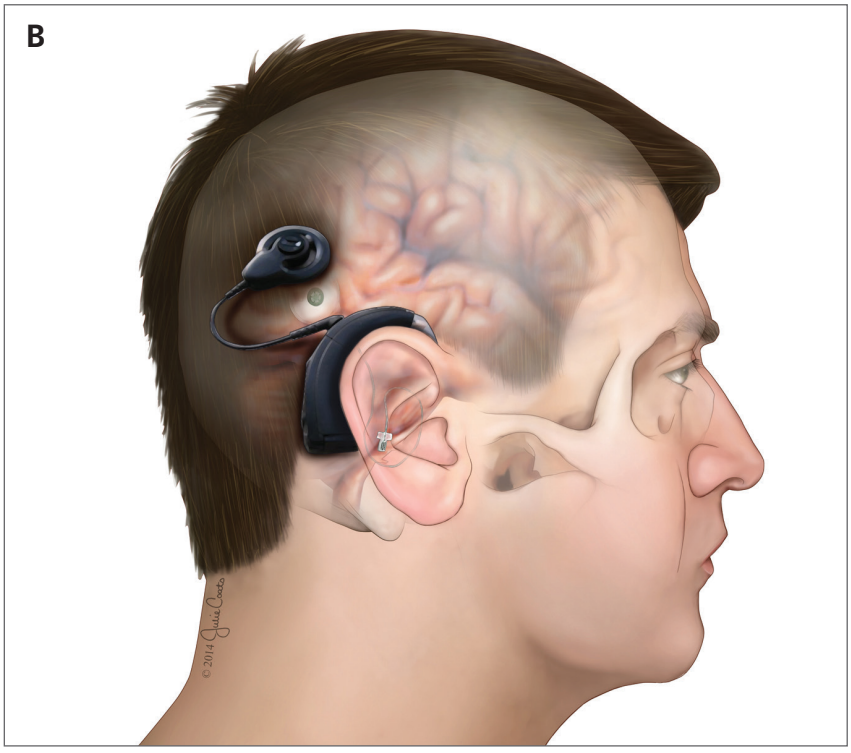


Figure 2: Illustration of (A) the intraoperative exposure during (B) implantation of the auditory brain implant and postoperative positioning. A translabyrinthine exposure results in identification of the foramen of Luschka (arrow), followed by placement of the paddle electrode under direct visualization.

Surgical Technique

The surgical approach for most NF2-related vestibular schwannomas is the translabyrinthine approach. This route also facilitates ABI via direct access to the pontomedullary junction. Because the cochlear nuclear complex is not visible on the surface of the brainstem, critical landmarks like the cerebellar peduncle, choroid plexus, lateral recess of the fourth ventricle, and foramen of Luschka must be identified for proper implant placement. A wide translabyrinthine exposure that includes decompression of the sigmoid sinus and jugular bulb is necessary to visualize these structures. The ideal implant location overlies the ventral cochlear nucleus due to its role as the primary relay for cochlear nerve input and the subsequent ascending auditory pathway.[13] This placement is accomplished by inserting the electrode through the foramen of Luschka and into the lateral recess of the fourth ventricle *(Figure 2)*.

Intraoperative cranial nerve monitoring serves as an important adjunct, especially when the anatomy is distorted by large tumors. Electrically evoked auditory brainstem responses, facial nerve monitoring, and glossopharyngeal nerve monitoring are all utilized. The cranial nerve status is of particular importance during electrode placement within the lateral recess. To confirm appropriate implant location, the device is stimulated intraoperatively. During this stimulation, electrophysiological monitoring can reveal whether nonauditory brainstem nuclei are erroneously activated; if they are, the implant can be readjusted. Once the correct position of the implant has been confirmed, it is secured in place with a piece of Teflon felt and packed into the meatus of the lateral recess. The electrode will eventually be encapsulated by fibrous tissue that adheres it against the brainstem. The receiver/stimulator is secured to the temporal bone in a manner analogous to a cochlear implant. The translabyrinthine defect is then closed in a multilayered fashion, which has previously been described following resection of vestibular schwannomas.[14,15]

Hearing Results and Future Direction

The hearing outcomes and speech perception for ABI users vary greatly and, in general, lag behind the robust results seen with cochlear implants. Still, the importance of restoring some degree of hearing function cannot be overstated. Identification of environmental sounds like smoke alarms, sirens, or horns can save lives. Often the ability to hear tonal elements of speech enables lip-reading and improved communication.

The functional outcome of an ABI user is complex and dependent upon both the physical and mental health of the recipient as well as the environment in which they live. The original data cited by the FDA for approval of the Nucleus 24 ABI System was based upon a case series of 92 patients with NF2, ages 12 and older.[16] This series reported 85% of patients were able to perceive some auditory sensations. Of the recipients who were able to have some degree of hearing restored, 93% had improved sentence understanding when they combined ABI usage with lip-reading compared to lip-reading alone. Other studies have supported the principle that ABI, when combined with lip-reading, improves sentence recognition, but very few ABI users will develop meaningful open-set speech with the ABI input alone.[17] It is also important to recognize that ABI users continue to improve their function years after using the device.

Currently, the majority of ABI recipients have been patients with NF2. A growing body of evidence suggests that other indications for ABI exist and, in fact, these non-NF2 recipients may have better outcomes than NF2 patients.[18] Much of this data is from Europe, and further support from other ABI centers throughout the world is necessary. Additionally, as researchers learn more about the inherent properties of the cochlear nucleus complex, engineers may better adapt the ABI technology for optimal stimulation of brainstem nuclei. Understanding differences between stimulation of the cochlear nerve and cochlear nuclei may unlock a new era of functional ABI.[6,19]

Conclusion

Use of ABI technology requires a complex multidisciplinary skull base surgery team to provide hope of hearing for patients with bilateral cochlear nerve destruction and deafness. Further study in functional and restorative neurosurgical applications is needed to expand the application of this and similar work.

The authors report no financial relationships with commercial interests relevant to the content of this article.

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Current Paradigms in the Treatment of Large and Giant Carotid Circulation Intracranial Aneurysms

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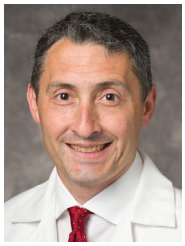

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Introduction

Throughout the past 20 years, the treatment of neurovascular pathology has taken great strides forward. This progress is particularly true with respect to endovascular treatments with the advent of Guglielmi detachable coils.[1] Even so, there remains no consensus on the treatment paradigm for the more complex vascular lesions, including the treatment of large and giant intracranial aneurysms (LGIA). Traditional open microneurosurgical technique for these aneurysms often includes parent occlusion and bypassing when necessary. Endovascular treatment has included coiling often with balloon or stent assistance. Newer stent designs have evolved to utilize flow-diverting modalities of which the only Food and Drug Administration (FDA)-approved device is the pipeline embolization device (PED). The PED works via an endoluminal approach to promote stagnation of flow and thrombosis within the aneurysm, while simultaneously maintaining patency of parent vessel and perforating vasculature.[2] Flow-diverting technology represents an exciting new tool for management of LGIAs because it appears to have very high occlusion rates similar to that of surgical treatment while ostensibly exposing patients to less morbidity than open surgical procedures. Real-world experience in clinical practice does not always reflect results present in the medical literature, which are often prone to bias in patient selection as well as industry pressure on study authors and reviewers.

In this article, we aim to review the pertinent literature, give a summary of the recent studies involving flow-diverting stents and share our initial experience of LGIAs. We frankly discuss our experience with the learning curve involved in utilizing this technology and compare our experience to similar cases treated microsurgically. All of the patients discussed in this article harbored aneurysms that met the manufacturer's and FDA's indications for use of the PED.

The Development of Flow Diversion Technology

When considering the newest generation of endovascular tools developed for the management of LGIAs of the carotid circulation, it is necessary to understand the mechanism of action of flow-diverting devices. Kerl and colleagues demonstrated that compression of flow-diverting stents (FDSs) relates in a linear fashion to the porosity of the device, which also correlates significantly with the amount of aneurysm inflow without affecting mean intra-aneurysm pressure.[3] This correlation is intuitive and is important when choosing the appropriate FDS to treat various aneurysms.

Originally, FDSs, such as the PED and SILK devices, were utilized to treat large and giant aneurysms unsuitable for other treatment modalities as well as those that have failed other treatments. It is worth noting that there has recently been a shift to include treatment of small- and medium-sized aneurysms also.[4,5] In a small four-patient study, Kim and colleagues demonstrated FDS function by altering the flow dynamics in the aneurysm by reducing intra-aneurysmal shear wall stress and the shear stress gradient, thereby promoting stasis.[6] Indeed, SILK has a similar profile to PEDs and is used in the European market for the treatment of giant aneurysms as well as fusiform aneurysms. The PED has also shown promise in the treatment of very small and blister aneurysms.[4,6] Criticism of this review stems from the unknown long-term durability of PEDs in aneurysms known to be amenable to coiling, which has a known and acceptable risk-to-benefit profile.[7]

The use and placement of PEDs have many challenges related to navigability of the longer stents necessary for treatment of LGIAs and challenges associated with landing and deploying the stents. They require a certain level of technical skill and finesse, and complications may arise from the complex vasculature, the need to utilize multiple catheters, and limitations in the device design itself.[7-9] Webster-Crowley and colleagues presented a case of a 70-year-old patient with a giant supraclinoid internal carotid artery (ICA) aneurysm treated with a PED that deployed incompletely and prolapsed into the aneurysm during positioning. A salvage technique was used to occlude the middle cerebral artery with a balloon, and traction was placed on the PED and realigned with the parent vessel without further incident.[9] Such complex recovery techniques are not uncommonly utilized in the placement of PEDs, and the difficulty inherent in such maneuvers may not be reflected in the complication rates reported in the literature.

Alternatively, microsurgical trapping and bypass of aneurysms has been an effective treatment method for many years.[10,11] Although additional morbidity is associated with open surgery and a degree of expertise is required, which limits widespread availability, in experienced hands and with adequate preoperative assessments of flow and circulation the long-term outcomes of microsurgery are excellent. Advantages include immediate aneurysm occlusion, which is permanent, as well as avoidance of complex antiplatelet medication regimens in contrast to PED treatment. In this article, we compare our initial experience with the PED to a similar series of patients treated with microsurgical trapping and bypass to provide an illustrative series of examples reflecting a real world experience in a large tertiary care academic practice. All patients were treated by the senior author (NCB) over a period of 2 years (2012 to 2014). In all cases, patients underwent preoperative balloon test occlusion evaluation to assess for collateral circulation, with concomitant nuclear medicine evaluation to assess cerebral vascular reserve. Additionally, patients who underwent placement of the PED were pretreated with aspirin and clopidogrel for 7 days prior to the procedure as long as they were found to be adequate responders on platelet aggregation assays.

Case Illustrations

Case 1

MF is a 47-year-old previously healthy female who presented with diplopia and was found to have a left abducens nerve palsy. Imaging demonstrated a left giant cavernous ICA aneurysm, which measured 25 mm in greatest diameter. The patient was admitted for elective occlusion with the PED after balloon test occlusion (BTO). The device was placed successfully, but during deployment the guidewire fractured and was retained beyond the device. The wire was unable to be retrieved despite multiple attempts and was left in place as it was not intraluminal or flow-limiting. The patient was started on heparin post-procedure and was later transitioned to a standard post-PED regimen of aspirin and clopidogrel and remained neurologically intact. At 6-month follow-up, the patient had a stable sixth nerve palsy while angiography demonstrated thrombosis of the aneurysm and stable appearance of the retained wire *(Figure 1)*.

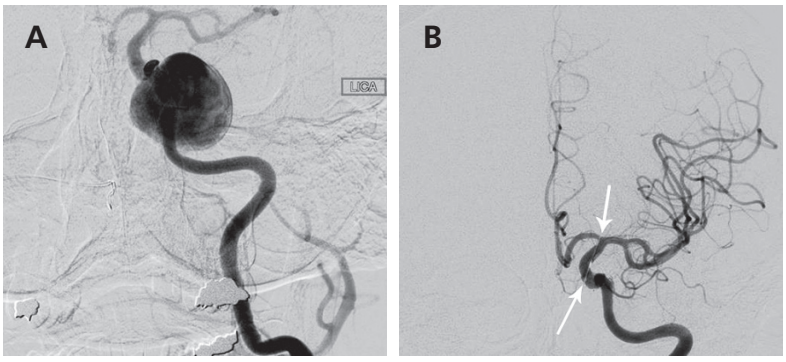

Figure 1: (A) Preoperative posteroanterior angiography of a giant left internal carotid artery aneurysm. (B) Posteroanterior and lateral films of a retained fractured catheter excluded from circulation following deployment of a pipeline embolization device (arrows).

Case 2

PC is an 81-year-old female with a history of a left giant ICA aneurysm who was admitted after an elective pipeline procedure. The procedure was complicated by premature deployment of the pipeline device with retraction into the aneurysm. After unsuccessful retrieval was attempted, the aneurysm was treated with coil embolization and occlusion of the left ICA, which resulted in punctuate ischemic changes on magnetic resonance imaging and mild right hemiparesis, which resolved over a period of 6 months, and the patient otherwise did well *(Figure 2)*.

Case 3

JH is a 57-year-old man who presented with transient diplopia and abducens weakness. He was found to have a right giant cavernous ICA aneurysm and underwent placement of a PED. Seven days after procedure, the patient developed headache, nausea, and vomiting. Computed tomography of the head demonstrated large right parieto-occipital intracerebral hemorrhage (ICH) *(Figure 3)*. The ICH necessitated emergent craniectomy and evacuation of hematoma, a prolonged rehabilitation, and subsequent surgery to replace the bone flap after several weeks. Despite these complications, he was functionally independent and at neurologic baseline at follow-up, with complete aneurysm thrombosis.

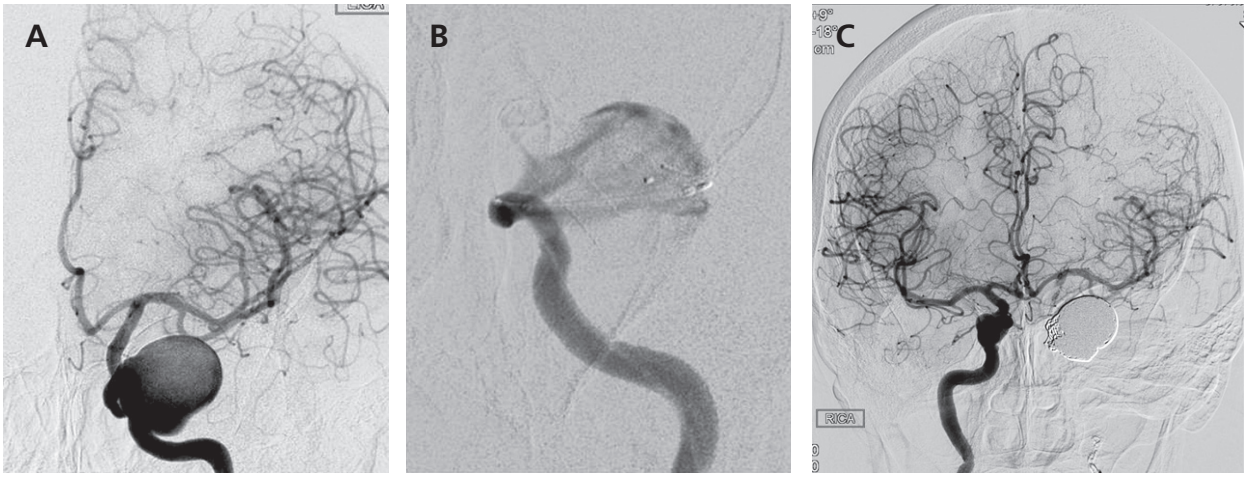

Figure 2: (A) Posteroanterior preoperative projection of a giant left internal carotid artery aneurysm (ICA). (B) Posteroanterior projection of a prematurely deployed pipeline embolization device within the aneurysm sac. (C) Postoperative posteroanterior projection of the sacrificed left ICA with coiling of the aneurysm and cross-filling of left-sided vasculature from the right ICA.

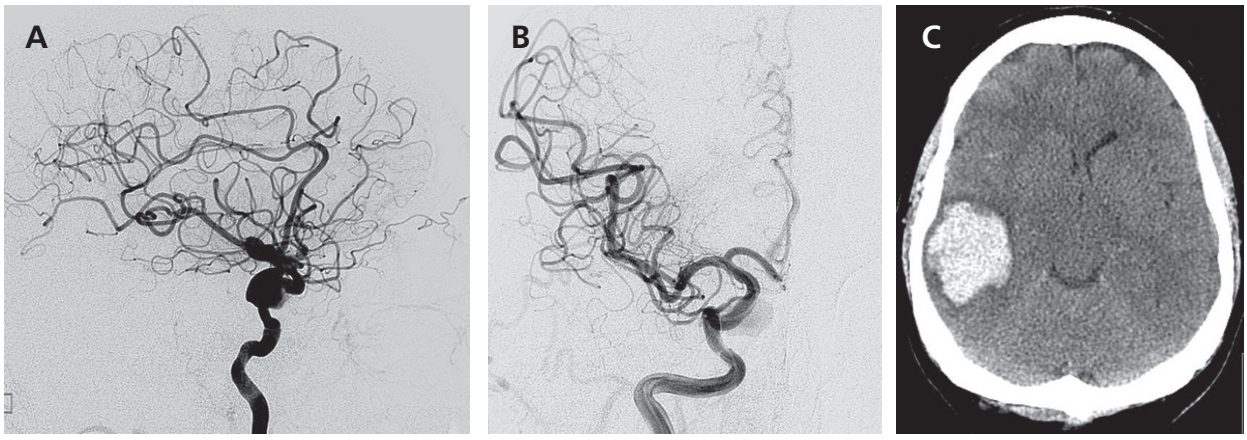

Figure 3: (A) Lateral angiography of a large fusiform internal carotid artery aneurysm. (B) Posteroanterior projection of occluded aneurysm after deploying a pipeline embolization device. (C) Ipsilateral intracerebral hemorrhage perioperatively, which required a decompressive craniotomy.

Case 4

RW is a 67-year-old woman with a history of hypothyroidism and hyperlipidemia who originally presented with 2-day history of right-sided headache and right eye ptosis. She was found to have a giant right ICA cavernous aneurysm. After BTO demonstrated good collateral reserve with mild impairment on nuclear spectroscopy within the right carotid artery territory, the patient underwent successful trapping occlusion of the ICA both proximally and distally followed by a superficial temporal artery to middle cerebral artery (STA-MCA) bypass. She tolerated the procedure well and had no postoperative neurologic sequelae.

Case 5

RB is a 37-year-old woman, previously healthy, who presented with headache, nausea, and vomiting. She was found to have a giant left cavernous ICA aneurysm. After being tested with BTO, the patient underwent craniotomy for trapping of the aneurysm both proximally and distally followed by an STA-MCA bypass. Postoperatively, the patient developed diminished visual acuity with central scotoma related to diminished flow within the ophthalmic artery. Ultimately, the patient maintained functional vision in the right eye with 20/40 acuity. Postoperative angiography demonstrated patent bypass grafting complete thrombosis of the aneurysm *(Figure 4)*.

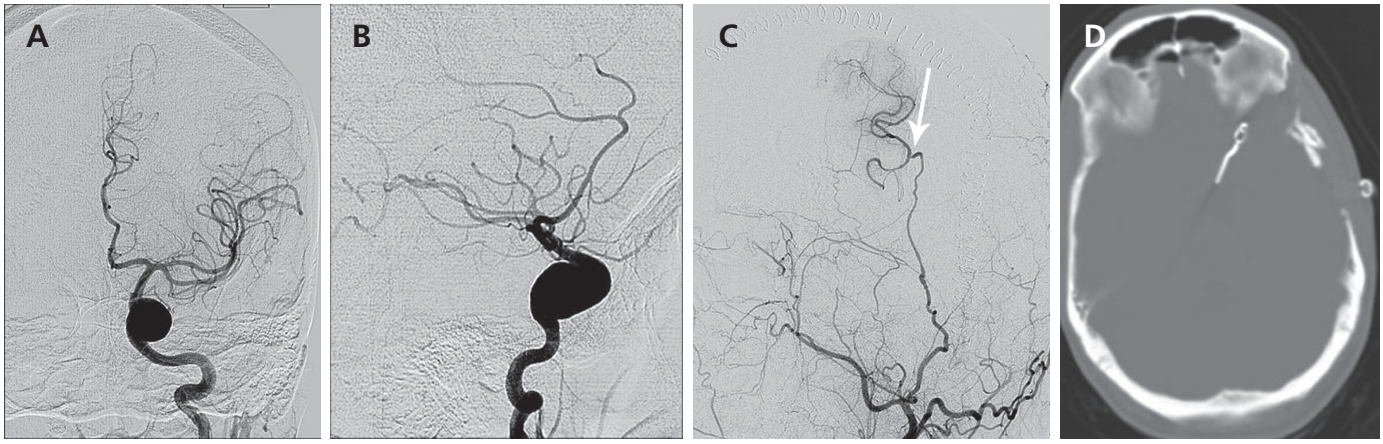

Figure 4: (A, B) Posteroanterior and lateral projections of a left internal carotid artery aneurysm treated with surgical trapping and bypass. (C) Postoperative projections of patent superficial temporal artery to middle cerebral artery bypass graft (arrow). (D) Axial computed tomography of bone windows demonstrates clip position occluding internal carotid artery distal to the aneurysm.

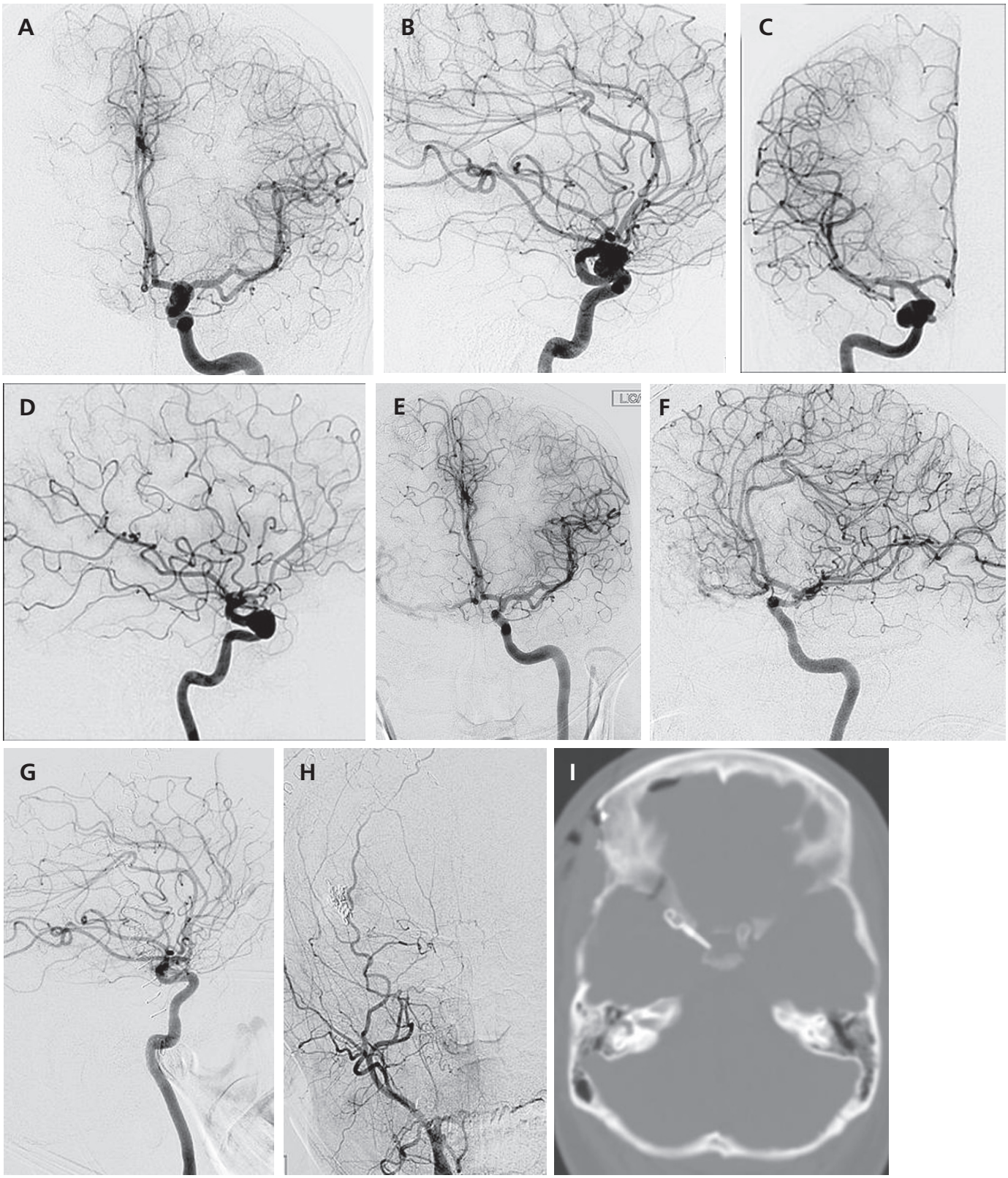

Figure 5: (A – D) Preoperative posteroanterior and lateral projections of a left fusiform internal carotid artery aneurysm and a right large internal carotid artery aneurysm. (E, F) Angiogram following placement of the pipeline embolization device shows aneurysm thrombosis and excellent flow through the carotid artery. (G, H) Angiogram following a superficial temporal artery to middle cerebral artery bypass and trapping of the right-sided aneurysm. (I) Axial computed tomography of the head bone windows demonstrates clip position occluding the right internal carotid artery distal to the aneurysmal segment.

Case 6

SB is a 76-year-old woman who presented with acute onset diplopia with left sixth nerve palsy, without nausea, vomiting, or headache. Imaging was positive for a large 22 mm left cavernous ICA aneurysm. The patient underwent successful BTO and ultimately underwent an STA-MCA bypass with trapping of the aneurysm. The patient tolerated the procedure well. Postoperative angiography demonstrated patency of bypass and aneurysm occlusion.

Case 7

CS is a 34-year-old woman with a long history of headaches, fibromyalgia, and blurry vision found to have bilateral giant ICA aneurysms. Given the patient's clinical findings, she first was treated with a PED for the left ICA aneurysm. Postprocedurely, she required several courses of oral steroid administration for severe ocular headaches as well as episodes of epistaxis and severe bruising as a consequence of prolonged dual antiplatelet therapy. Nevertheless, at 12 months angiography, she demonstrated thrombosis of the left ICA aneurysm *(Figure 5)*. After discussing further treatment options, the patient elected to undergo a right-sided STA-MCA bypass and open surgical trapping for the right aneurysm. She did well following this procedure and required no further treatment.

Discussion

The process of aneurysm occlusion involves three primary processes: thrombus formation, diversion of blood flow, and neo-intimal formation. The process may be accomplished with surgical clipping, coil embolization, stent-assisted coil embolization, or flow diversion. In appropriately selected patients, microsurgical management of LGIAs can be extremely effective. In a series of 51 patients, 43 were directly clipped, 7 were trapped with an extracranial to intracranial bypass, and 1 had only proximal ICA ligation.[10] Long-term outcomes were excellent with mRS < 2 in 90% of patients.[10] This series notes the success of these approaches, coupled with the importance of multimodality monitoring and surveillance intraoperatively with indocyanine green angiography, extremity and facial corticobulbar motor evoked potentials, and somatosensory evoked potentials.[10,12] A recent review at Barrow Neurological Institute reported > 80% good outcomes in 56 patients similarly treated with open surgical trapping and bypass, with an overall mortality of 12% and morbidity of 15%.

In 2014, Li and colleagues compared coiling, parent artery occlusion (PAO), and balloon deployable stenting for the treatment of LGIAs, and all modalities demonstrated effective treatment with good outcomes and minimal associated morbidity.[13] However, recurrence of treated aneurysms after endovascular coiling treatment is reported to occur in 9% to 43% of cases,[13,14] thought to occur secondary to recanalization as well as coil compaction and is significantly more common in LGIAs than in smaller aneurysms. Coiling may also propagate symptoms of mass effect, and neurological sequelae are not uncommon.[13] Contrary to these findings, Hassan and colleagues in 2013 reported on improvements of mass effect symptoms and cranial neuropathy following coiling and PAO, which is comparable to clipping.[15] In the recent MAPS trial, the recurrence rate of coiled aneurysms was reinforced at a rate of approximately 30% in this trial; the matrix polymer modified coils were found to have similar rates of recurrence with traditional coils, with the theoretical benefit of promoting more stable occlusion after treatment.[16] These results have tempered enthusiasm for coil occlusion of giant aneurysms, leading to the current trend favoring flow diversion as an alternative.

Morbidity associated with FDSs includes intraparenchymal hemorrhage, delayed hemorrhage, in-stent stenosis, and occlusion of perforating vessels as well as parent vessels. Given the concern for embolic complications, testing for clopidogrel responsiveness is generally utilized.[17] The reported incidence of ischemic complications varies wildly over a range of 3% to 30%.[3,4,9,18-20] In contrast, severe hemorrhagic complication rates for FDSs are from 0.8% to 2%. Though less common, hemorrhagic complications are often devastating and reported to be associated with a 0.75% permanent morbidity and 1% to 5% mortality. The cause of the latter complication is unclear and is secondary to the need for dual antiplatelet therapy compounded by endoluminal leakage or emboli of catheter coatings during the procedure.[4,9,18,20,21]

Of concern is that the overall complete thrombosis rate of LGIAs treated with a PED is variable and not immediate. Changes in aneurysm size often reflect the dynamic process involved in aneurysm thrombosis,[19] and there is evidence to suggest that an increase in the size of the aneurysm reflects incomplete exclusion of the aneurysm from the circulation. Failures despite optimum deployment of a PED are difficult to explain but have been postulated to be secondary to poor patient compliance, anomalies of blood flow, or instability of intra-aneurysm thrombus. In multiple studies, the recurrence rate of aneurysms treated with a PED has ranged from 5% to 53%.[4,22-26]

At present there are no proven predictors of aneurysm occlusion, although aneurysm perfusion noted in the periprocedural window as well as the amount of contrast stasis in the aneurysm may be predictive of thrombus formation. To avoid procedural and ischemic complications, there has been a trend toward placement of fewer total PEDs resulting in lower aneurysm thrombosis rates in the immediate postprocedural period. Other important factors in aneurysm thrombosis include patient coagulation and antiplatelet status, morphology of the aneurysm, size of the aneurysm, flow dynamics in associated vasculature, and prior failed treatment with residual coil/stents in

place.[4,20] The most optimistic reports of aneurysm occlusion rates have them at more than 90% at 12 months *(Table 1),* which is in stark contrast to the 66% of those treated with coiling. It must be recognized that many if not most of the aneurysms treated in these large series would be considered off-label by the FDA and are often smaller and thus easier to treat.

Finally, a conversation regarding the current state of affairs for treating LGIAs would not be complete without the discussion of cost. While there is a large disparity of cost when treating smaller aneurysms, the cost of endovascular treatment for aneurysms greater than 12 mm is essentially the same regardless of the method used.[26] Colby and colleagues report a reduction in cost of 27% when compared to stent-assisted coiling per 1 mm of aneurysm treated.[27] Understandably, the cost is more noticeable with larger aneurysms and, in terms of implant costs, far exceeds the cost of surgical treatment. Whether this cost disparity is eliminated when factoring the higher hospital costs incurred with open surgery is unclear.

Conclusion

With newer therapeutic devices becoming available, the treatment of large and giant intracranial aneurysms has increasingly favored a flow-diverting therapy. While most studies have reported acceptable complication rates as illustrated with the cases in this article, the learning curve associated with newer devices such as the PED must be considered in treatment decisions. Though more invasive, open surgical treatment remains a durable and safe procedure in experienced hands and should remain an option in the treatment of LGIAs for the foreseeable future. Regardless of the modality utilized in any particular patient, these procedures are quite difficult and complex and we believe should be performed by experienced practitioners at high-volume tertiary centers where cerebrovascular neurosurgical expertise is readily available. Further, when deciding on treatment for patients with LGIAs, one must consider the patient, the presenting symptoms (e.g., rupture or mass effect), and the comfort and experience of the provider. As the trend toward endovascular treatment continues, we must temper our enthusiasm and continue to act in the best interest of our patients who entrust us to recommend the safest and best long-term treatment modality available.

Table 1: Summary of recent studies investigating pipeline embolization device, including success rate and complication rates reported in percent of patients with said complications

Study	Number of patients	Number of aneurysms successfully treated	Hemorrhage (SAH and ICH) (%)	Stroke (%)	Morbidity/ mortality (%)	Aneurysm obliteration (%)
Lylyk et al., 2009 [22]	53	63	0	0	0	94
Szikora et al., 2010 [23]	18	19	6	11	17	94
Nelson et al., 2011 [24]	31	31	3	3	6	100
Lubicz et al., 2011 [25]	20	27	5	5	10	84
Chitale et al., 2012 [28]	36	42	11	6	19	85
Colby et al., 2012 [27]	34	41	3	0	3	NA
Deutschmann et al., 2012 [29]	12	12	0	0	0	100
Gupta et al., 2012 [35]	88	101	3	2	7	73
Kan et al., 2012 [30]	56	58	7	2	9	68
McAuliffe et al., 2012 [31]	54	57	0	0	0	86
McAuliffe and Wenderoth, 2012 [32]	11	11	18	0	18	89
O'Kelly et al., 2012 [33]	94	94	7	1	4	82
Saatci et al., 2012 [20]	191	251	1	<1	2	92
Yu et al., 2012 [34]	143	178	2.7	<1	3	85

SAH = subarachnoid hemorrhage; ICH = intracerebral hemorrhage

Jonathan Pace, MD, discusses unlabeled/investigational uses of a commercial product in this article. Kristine Blackham is a primary investigator for Hospira, Inc., though this relationship has not affected the content of this article and the CME Program has determined there is no conflict of interest. The other authors report no financial relationships with commercial interests relevant to the content of this article.

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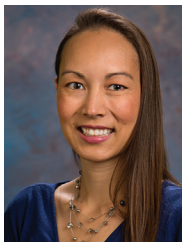
Intraoperative Spinal Neuromonitoring – Indications and Patterns of Usage Among Neurosurgeons

Authors



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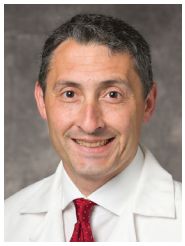

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On behalf of the Medicolegal Committee of the Council of State Neurosurgical Societies

Introduction

Neurophysiologic intraoperative monitoring (NIOM) in spinal surgery is intended to monitor neural structures at risk during these operations. First reported using somatosensory evoked potentials (SSEPs),[1] spinal NIOM incorporated motor evoked potential (MEP) monitoring following the appreciation of false negative risk with SSEPs alone, once MEPs could be performed under anesthesia.[2] Use of SSEPs and MEPs together, often with the inclusion of concurrent electromyography (EMG) recordings from myotomes at the level of spine surgery, is commonly referred to as multimodality monitoring. At present, while there are numerous case series suggesting efficacy of multimodality NIOM for prevention of new neurologic deficits, none is of methodological rigor sufficient enough to establish an unassailable evidentiary basis for declaring that NIOM has preventive value. This evidence gap finds direct expression in two practice guidelines: the American Academy of Neurology's evidence-based guideline on NIOM, which is careful to state that spinal NIOM has predictive but not preventive value,[3] and the joint spine surgery practice guidelines of the American Association of Neurological Surgeons (AANS) and the Congress of Neurological Surgeons, which categorize NIOM as a practice option but stop short of a positive recommendation for preventing complications.[4,5] Currently, from a surgeon's perspective, there is no existing standard of care regarding NIOM.[6] We sought to clarify current patterns of practice among neurosurgeons who perform spine surgeries and to assess variables associated with the use of various NIOM modalities as well as surgeons' reasons for incorporating these modalities.

Methods

We sent a survey to all AANS member and nonmember neurosurgeons in the United States and assessed the frequency of use of intraoperative neuromonitoring for the following categories of spinal operations: anterior cervical decompression and fusion, posterior cervical decompression and fusion or laminoplasty, anterior thoracic decompression with or without fusion, posterior thoracic decompression with or without fusion, posterior lumbar discectomy, posterior lumbar decompression without fusion, anterior lumbar interbody fusion, posterior lumbar decompression and fusion with or without interbody graft, spinal deformity correction, and surgery for tumor or vascular malformation. We inquired as to the frequency with which the operating surgeon utilized intraoperative neuromonitoring and allowed respondents to answer with one of the following: always, usually, sometimes, rarely, never, or not applicable.

Results

Of 4,488 surveys sent, we received responses from 683 individuals – a 15% response rate. The responses represented a variety of practice types (15.8% in solo practice, 53.5% in private practice, and 30.1% in academic practices) and practice locations. The respondents varied in the proportion of their practice that consists of spine surgery as well as the level of subspecialty spine training (19.3% of respondents indicated completion of a spine fellowship).

We noted several trends in our data. Consistent with previous surveys of spine surgeons,[7-9] intraoperative monitoring occurred most often in spinal deformity correction surgery (62% of surgeons performing that procedure answering always) and surgery for tumor and vascular malformation resection (59.7% of surgeons performing that procedure answering always). For the purpose of our statistical analysis as well as discussion, we regard "always" and "usually" to be frequent use of neuromonitoring and "sometimes," "rarely," and "never" to be infrequent use of neuromonitoring. For both anterior and posterior cervical procedures, despite "always" being the most common response, responses of "sometimes," "rarely," or "never" totaled 64.4% and 57.7% for anterior and posterior approaches, respectively. For thoracic procedures, 57.5% of surgeons performing anterior thoracic procedures cited frequent use, whereas only 47.1% cited frequent use for posterior thoracic procedures. Posterior lumbar decompression and lumbar discectomy were noteworthy for particularly low use of neuromonitoring with 63.2% and 69.4% of surgeons performing those procedures responding that they never used neuromonitoring. Considering all answers consistent with infrequent use of monitoring, 85% of surgeons performing lumbar decompression without fusion and 87.8% of surgeons performing lumbar discectomy cite infrequent use. Anterior lumbar interbody fusion displayed low rates of neuromonitoring, with 68.5% of surgeons performing that procedure using monitoring infrequently.

Posterior lumbar decompression with or without interbody graft demonstrated only 45.7% of surgeons perform the procedure frequently using monitoring.

We also assessed the modality of intraoperative monitoring used, asking respondents to indicate which modalities were used for each surgery they performed: SSEP, MEP, EMG, or other modes. For anterior and posterior cervical surgery, anterior and posterior thoracic surgery, deformity correction surgery, and surgery for tumors or vascular malformations, SSEP was the most frequently used modality, with MEP as the second most frequent modality and EMG third. EMG was the most frequently used modality followed by SSEP and then MEP for posterior lumbar surgeries, including discectomy, decompression, and posterior lumbar fusion with or without interbody graft. Anterior lumbar surgery demonstrated SSEP as the most frequent modality followed by EMG and then MEP. Overall, SSEP was the most frequently used modality. However, respondents indicated unimodal utilization, without at least one other modality, only rarely; the most frequent combinations were SSEP/MEP and SSEP/MEP/EMG. Utilization of all three modalities was most common for anterior and posterior cervical surgery, surgery for deformity correction, and surgery for tumors and vascular malformations. Utilization of SSEP and MEP was most common for anterior and posterior thoracic surgery. Utilization of SSEP and EMG was most common for anterior lumbar surgery, lumbar discectomy and decompression, and posterior lumbar fusion, though posterior lumbar fusion demonstrated a similar number of respondents utilizing only SSEP/EMG and those using all three modalities.

Though we did not survey minimally invasive spine (MIS) procedures as a separate procedure, we did question whether MIS altered the use of neuromonitoring. Only 106 (17.6%) respondents stated that MIS would change the frequency of use of neuromonitoring; 494 (82.3%) of respondents stated it would not change the frequency of use. Of those who claimed it would change frequency, 87 (79.8%) of respondents stated it would increase use, and 22 (20.2%) stated it would decrease use.

Utilizing the same categories of frequent and infrequent monitoring, we attempted to discern if the completion of a spine fellowship altered the use of neuromonitoring. Using a chi-squared analysis, we noted differences at the 95% significance level (uncorrected) in frequency of monitoring use for spine fellowship-trained surgeons versus nonspine fellowship-trained surgeons for the following surgeries: anterior cervical discectomy, posterior cervical decompression and fusion or laminoplasty, posterior thoracic decompression with or without fusion, and deformity correction *(Table 1)*. While formal Bonferroni correction for multiple comparisons would render these P values greater than 0.05, the values remain suggestive of real differences in practice patterns for fellowship-trained spine surgeons.

Survey: medicolegal impact

Our survey contained several questions regarding the medicolegal implications of intraoperative neuromonitoring in spine surgery. Specifically, we asked if respondents were ever involved in a lawsuit where neuromonitoring was a claim, whether the judgment favored the plaintiff, what the allegation regarding neuromonitoring consisted

Table 1. Comparison of monitoring frequency for spine fellowship-trained versus nonspine fellowship-trained neurosurgeons

Procedure	Chi-squared value	P-value	Odds ratio	95% CI
Anterior cervical discectomy and fusion	5.6921	0.017	1.63	1.09,2.45
Posterior cervical	4.256	0.039	1.52	1.01,2.27
Anterior thoracic	0.0023	0.962	not applicable	
Posterior thoracic	4.5983	0.032	1.55	1.03,2.33
Anterior lumbar interbody fusion	0.1931	0.66	not applicable	
Lumbar discectomy	0.2202	0.639	not applicable	
Lumbar decompression	0.9255	0.336	not applicable	
Posterior lumbar interbody fusion	0.1122	0.738	not applicable	
Deformity correction	5.1071	0.024	2.3	1.10,4.83
Tumor or vascular malformation	2.9336	0.087	not applicable	

CI = confidence interval

of, and whether fear of litigation contributes to the use of neuromonitoring. Thirty-eight (6.3%) of respondents stated that they had a previous lawsuit where monitoring was a part of the claim. Of those individuals, 47.5% of the judgments favored the plaintiff. The most frequent claim was lack of neuromonitoring in 13 judgments, and the second most frequent claim was failure to respond to changes in neuromonitoring in three judgments. (The remaining three individuals with judgments favoring the plaintiff did not respond to these questions.) Fear of litigation contributed to use of monitoring according to 54.4% of respondents.

Discussion

As is common to surveys of professionals, ours was limited by low response rate and resulting sample size. We therefore cannot confidently assess covariates such as practice type, proportion of spine surgery done in practice, and geographic location. A larger survey response would be necessary to perform a logistic regression, which could assess for strength of association with such factors. Our respondents represented a variety of practice types and locations as well as varying levels of spine surgery being incorporated into training and practice; however, given our response rate, we were unable to ascertain that these results hold true to the population of spine surgeons at large. Additionally, our survey included only members and nonmembers of the AANS and may not appropriately represent orthopaedic-trained spine surgeons. Still, to our knowledge, our survey remains the largest survey of spinal surgeons on this topic yet published.

Our findings confirm and expand considerably on prior spine surgeon surveys.[7-9] The finding that fellowship-trained spine surgeons are more likely to utilize monitoring reproduces the results found by Magit and colleagues.[7] Our results regarding utilization rates by procedure type broadly recapitulate that survey as well as that of Peeling and colleagues in finding high rates of reported use in spinal tumor and deformity correction cases, low rates with lumbar instrumentation, and intermediate rates with thoracic procedures[9]; we also reproduce their results in finding SSEPs used most frequently, MEPs next most, and EMG least often. Our quantification of frequency of use is novel compared to the prior surveys, which assayed a simple "yes" or "no" for use.

Also contrasting previous results, we found that the majority (54%) of respondents reported that utilization of neurophysiologic monitoring was in some part driven by malpractice concerns. To our knowledge, only Peeling and colleagues previously surveyed this exact issue, with a reported result of only 12%. This strikingly different rate may relate partly to the population in question because Peeling and colleagues surveyed Canadian surgeons, but the difference may relate to the question asked. Our survey asked only whether litigation concerns contributed at all, whereas Peeling and colleagues asked, "What is the main reason you use spine monitoring?" That caveat aside, our respondents' high rate of reported consideration of malpractice when deciding whether to monitor is properly surveyed confirmation of a phenomenon we have long suspected. With the recognition that there are no official standards in place regarding the utility or indications of neuromonitoring in spinal surgery and ongoing controversy regarding efficacy for prevention of new neurologic deficits,[4,5,10] there can be no firm recommendations regarding use of monitoring either in protecting practitioners from legal liability or predisposing them to a malpractice judgment or settlement against them. Though anecdotally cited as a cause of increasing liability in cases where monitoring was not utilized or in which changes occurred and in which permanent neurological morbidity was the outcome, a review of the available literature on the subject does not indicate that such an assumption is currently valid. Though it may form a portion of a plaintiff's allegation regarding malpractice, it does not appear that the use or interpretation of monitoring as a sole allegation is a significant cause of malpractice verdicts or settlements.[11-13] In Epstein's review of 54 cases with 146 associated allegations involving quadriplegia following cervical spine surgery over a 20-year period in six states, only three allegations were related to monitoring.[11] Of these three, two allegations involved failure to perform intraoperative monitoring while one case alleged a failure to treat intraoperative SSEP changes. Far more common were allegations of negligent surgery (47 allegations), failure to diagnose/treat (33 allegations), lack of informed consent (23 allegations), and failure to brace (15 allegations).[11] In summary, from a surgical perspective, it seems to us safest at present to presume that judicious use of monitoring in cases where the treating surgeon feels its use is clinically indicated should remain the best recommendation without regard to medicolegal concerns. Until the completion of methodologically sound prospective trials that permit the design of evidence-based practice guidelines, monitoring decisions must be based on each surgeon's judgment.

Conclusion

Use of spinal neuromonitoring has been exhaustively studied in the literature and has become widely utilized during spinal surgery. Our survey demonstrates a variety of practice patterns for intraoperative neuromonitoring, with certain trends noted. Though no standards of care exist regarding the use of neuromonitoring, several guidelines exist that may result in improved patient outcomes. Judicious use in line with these guidelines will most likely result in the best opportunity to ensure Medicare and third-party payer coverage, though such determinations are local. Taken in isolation, the use of monitoring or the response to monitoring interpretations is unlikely to affect the result of medicolegal cases of malpractice in spinal surgery. Nevertheless, fear of litigation impacts the use of spinal neuromonitoring, potentially contributing to its overuse without firm evidence of substantial benefit in certain cases.

The authors report no financial relationships with commercial interests relevant to the content of this article.

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Effects of Maternally Transmitted mtDNA Mutators

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Introduction

The discovery of mitochondria was made almost 170 years ago, only a few years after the discovery of the cell nucleus. Despite the long-standing recognition of these intracellular structures, the understanding of their function was revealed only much later because of a lack of methodological techniques. They were initially referred to "bioblasts," assuming that they were separate organisms living inside the cells. The term "mitochondrion" was finally introduced 50 years later from the Greek "mitos" meaning "thread" and "chondrion" meaning "granule," referring to the histological appearance of these structures. The idea that mitochondria were associated with cell respiration was not presented until 1912, but the data were based almost exclusively on morphological observations without biochemical evidence. It wasn't until the 1950s that mitochondria were finally recognized as the primary source of intracellular energy.

Almost all eukaryotic cells, including fungi, animals, and plants, contain mitochondria in the cytoplasm that produce energy in the form of adenosine triphosphate (ATP) from the oxidation of molecules, including proteins, lipids, and polysaccharides, which are broken down and enter the Krebs cycle. The high energy bonds in ATP power nearly all energy-dependent cellular processes. Additionally, mitochondria are involved in a range of other processes, including signaling, cellular differentiation, cell death, the control of the cell cycle, and cell growth.

It is hypothesized that aerobic eukaryotic cells evolved from symbiosis 1.5 – 2 billion years ago when aerobic eubacteria were engulfed by an ancestral anaerobic eukaryotic cell. This Endosymbiotic Theory was first proposed in 1905. These bacterial ancestors of mitochondria initiated a symbiotic relationship by providing large amounts of energy in exchange for shelter and nourishment from the eukaryotic cell. Approximately 10^9 molecules of ATP are found at any time per cell and are turned over every 1 to 2 minutes. Support for this theory, in part, derives from the strong resemblance between the circular DNA structure in mitochondria and that in bacteria.

Mitochondrial DNA of Mammals

Mammalian mitochondrial (mt) DNA contains only 37 genes that encode 13 mRNAs (all translated to parts of respiratory complex proteins). All other genetic information necessary for mitochondrial structure and the expression and maintenance of mtDNA are derived from nuclear DNA. The inheritance of mtDNA in mammals is considered to be strictly maternal contributed by oocyte mitochondria. The 13 mtDNA polypeptide genes encode 7 of the approximately 45 subunits of complex I, 1 (cytochrome *b*) of the 11 subunits of complex III, 3 (COXI-III) of the 13 subunits in complex IV, and 2 (ATPase6,8) of the approximate 17 subunits of complex V (ATP synthase). Complex II is entirely encoded by the nuclear genome. Mitochondrial DNA is approximately 16.5 kb in size in mammals and is a closed-circular double-stranded molecule, present as multiple copies, normally 1,000 – 10,000 molecules per cell. The mtDNA is very compact and consists almost exclusively of coding regions with no introns – the exception being the approximately 1 kb long displacement loop (D-loop) region, which is important for initiation of replication and transcription.

Mammalian mtDNA replication takes place in the mitochondrial matrix and is independent of cell cycle. The mutation rate of mtDNA is approximately 10-fold higher in mtDNA than in nuclear (n) DNA. Furthermore, because mtDNA has no introns or noncoding sequences, a mutation is more likely to influence function. Altered mtDNA can consist of point mutations, deletions, or duplications, and can be deleterious, beneficial, or neutral. The mitochondrial genome continues to replicate in both mitotic and meiotic cells; therefore, mtDNA mutations may be transmitted through the maternal germline. Point mutations are most often maternally transmitted, whereas the deletions are thought to be sporadic. Moreover, mtDNA and mitochondria are rapidly turned over in post-mitotic cells, with new mitochondria continuously synthesized and rapid destruction of older mitochondria, a process termed "mitophagy." There is also constant fusion and fission of these organelles under the control of various intracellular proteins, all of which can contribute to clonal expansion of the mutant mtDNA over time, though this process can also facilitate removal of abnormal mitochondria. This latter process is termed "purification."

More than one species of mtDNA can be found in individual cells, a state known as heteroplasmy. When a heteroplasmic cell divides, the distribution of wild-type and mutant mtDNA into the daughter cells is random, which can ultimately lead to segregation of the wild-type and mutant mtDNA, referred to as homoplasmy. mtDNA mutations can disrupt mitochondrial function if the amount of mutant mtDNA per cell reaches a threshold where inadequate functional mitochondria remain, unable to perform enough ATP generation. Thus, effective and faithful mtDNA replication is essential for cellular homeostasis and survival.

Challenges and Mutations

As the average age of the Western world population is increasing, many countries are predicting significant demographic changes over the next two to three decades. In the United States, the older population, defined as persons 65 years or older, is expected to grow to be 19% of the population, an approximate 7% increase since the year 2000. Europe is also facing significant changes, with a projected increase to 30% of the aged population by 2030. The consequences of the aging population will be one of the greatest challenges that the Western world will face from both a social and economic point of view. It is often referred to as a global aging epidemic as many age-related disorders, in particular degenerative diseases affecting various organ systems (brain, cardiovascular, musculoskeletal, renal, hematopoietic, etc.), are often associated with increased risk of disability. Consequently, there is an increased effort to understand the underlying mechanisms of the aging process, with the hope that aging per se does not necessarily have to include the various age-related afflictions and overall decline in health.

As noted above, there are 1,000 to 10,000 copies of mitochondrial DNA (mtDNA) per cell. The DNA polymerase gamma (Polg) is the only DNA polymerase found in mitochondria, and it is critically involved in replication and repair of mtDNA, acting as a proofreading enzyme to reduce replication of mutant mtDNA. Although there has been much data suggesting a mitochondrial influence on aging, because of the accumulation of mutations, the rate of endogenous mitochondrial DNA point mutations and deletions has made problematic the experimental tests of this mitochondrial hypothesis. However, in 2004, Trifunovic and colleagues developed the mtDNA mutator mouse: a unique test for the mitochondrial theory of aging.[1] The test was based on a homozygous knock-in transgenic mouse expressing a proofreading deficient version (D257A) of the nucleus-encoded catalytic subunit (PolgA) of mtDNA polymerase, which impairs proofreading during mtDNA replication. The mtDNA mutator mouse has a 3- to 5-fold increase in point mutations as well as increased levels of mtDNA deletions *(Figure 1).* The mtDNA mutator mice show premature onset of age-related phenotypes, such as anemia, reduced fertility, enlarged heart, alopecia, kyphosis, sarcopenia, hearing loss, reduced lifespan, subcutaneous fat, renal atrophy, and increased cell death via apoptosis *(Figure 1 and Figure 2)*. Interestingly, this premature aging

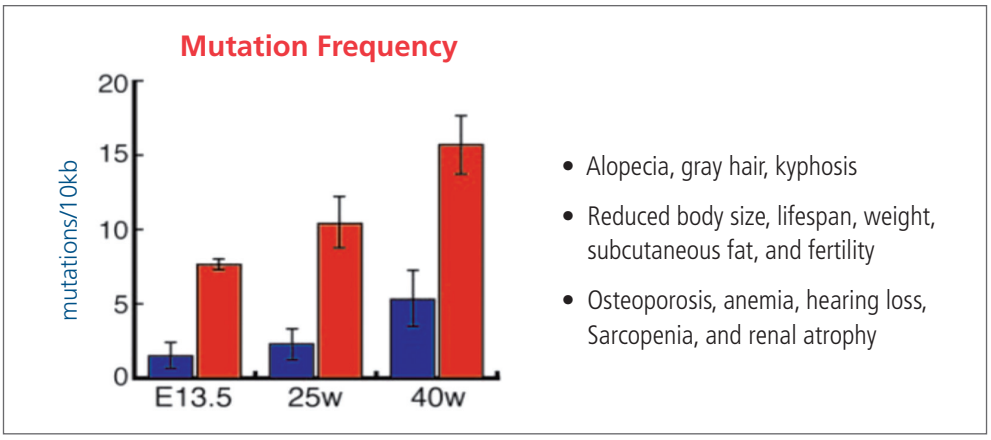

Figure 1: Mutation frequency in standard mtDNA mutation mice (red bars) compared with wild-type mice (blue bars).[1]

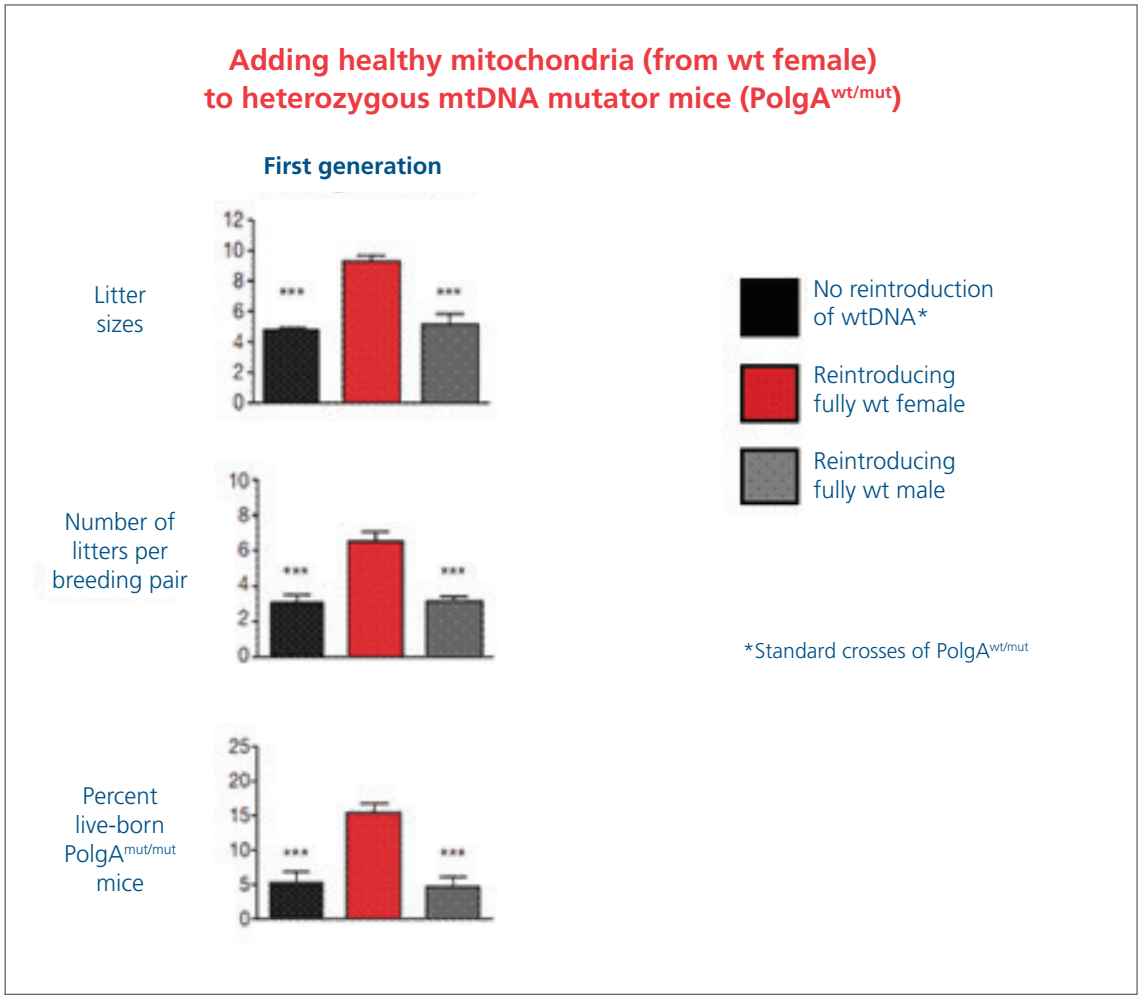

Figure 2: Examples of aging phenotypes in standard mtDNA mutator mice and its reversal by adding wild-type female healthy mitochondria.[2]

Genotype	PolgA$^{wt/wt}$	PolgA$^{wt/mut}$	PolgA$^{mut/mut}$	PolgA$^{wt/wt}$	PolgA$^{wt/mut}$
Maternally transmitted mtDNA mutations	+	+	+	–	–
Somatic mtDNA mutations	–	+	+	–	+
Mouse type	I	II	III	IV	V

Figure 3: Breeding scheme to generate wild-type variants. Mice heterozygous for the mtDNA mutator allele (PolgA$^{wt/mut}$) were intercrossed to generate Type I (PolgA$^{wt/wt}$), Type II (PolgA$^{wt/mut}$), and Type III (PolgA$^{mut/mut}$) mice, all with inherited germline mtDNA mutations from their heterozygous (PolgA$^{wt/mut}$) mother. Type II (PolgA$^{wt/mut}$) and Type III (PolgA$^{mut/mut}$) mice also formed *de novo* somatic mtDNA mutations. Male Type II (PolgA$^{wt/mut}$) mice were crossed with female wild-type mice to generate Type IV (PolgA$^{wt/wt}$) and Type V (PolgA$^{wt/mut}$) mice, both without inherited mtDNA mutations.[3]

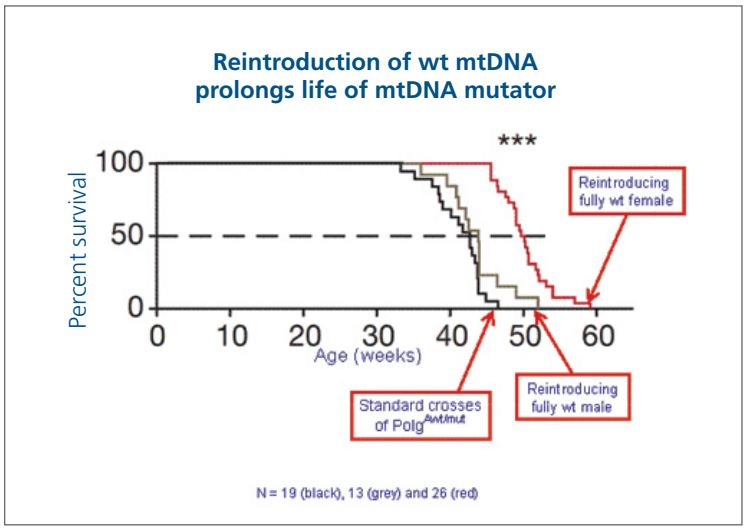

Figure 4: Longevity in mice with wild-type nuclear genomes is shortened by germline inherited mtDNA mutations. Type I wild-type mice (both males and females) obtained from standard intercrosses of PolgA$^{wt/mut}$ mice (black line, n = 13) with maternally transmitted mtDNA mutations have a significantly reduced lifespan ($X^2(1) = 24.4$). Significances were determined by the Mantel-Cox test, *** $P < 0.0001$. Reintroduction of wild-type mtDNA from females (red line), but not males (tan line) prolongs life of mtDNA mutator.[3]

phenotype does not appear to be tightly linked to changes in reactive oxygen species but rather is explained by a decline in oxidative capacity and energy production. Recent studies suggest that the stem cell niches in the mtDNA mutator mice are severely affected and may give rise to the anemia observed in these mice and contribute to the progeroid phenotype. There are also changes in lactate metabolism, suggesting that this molecule may be a biomarker for age-related changes in brain and peripheral organs.[2]

There are two sources of mtDNA mutations: germline, inherited from the mother that can have early prenatal effects, and somatic, caused during one's lifetime. These mutations are mosaic in nature and increase with age as cells and mitochondria replicate. To understand the role of germline transmitted vs. somatic mtDNA mutations for fertility, brain development, and aging phenotypes, we analyzed different genetically defined types of mice with aggravated germline and/or aggravated somatic mtDNA mutational loads, derived from crossings of mice with mutated PolgA.[3] The scheme for these crossings produces mice with differential germline vs. somatic mtDNA mutations *(Figure 3)*.[3]

Our results show that maternal inheritance of germline mtDNA mutations causes anticipation of reduced fertility, aggravates aging *(Figure 2)*, and shortens lifespan *(Figure 4)*. Moreover, adding healthy mitochondria (from a wild type [wt] female) to heterozygous mtDNA mutator mice (PolgA$^{wt/mut}$) can reverse this aging phenotype *(Figure 2)* and prolong lifespan *(Figure 4)*. Thus, it is important to start life with healthy mitochondria.

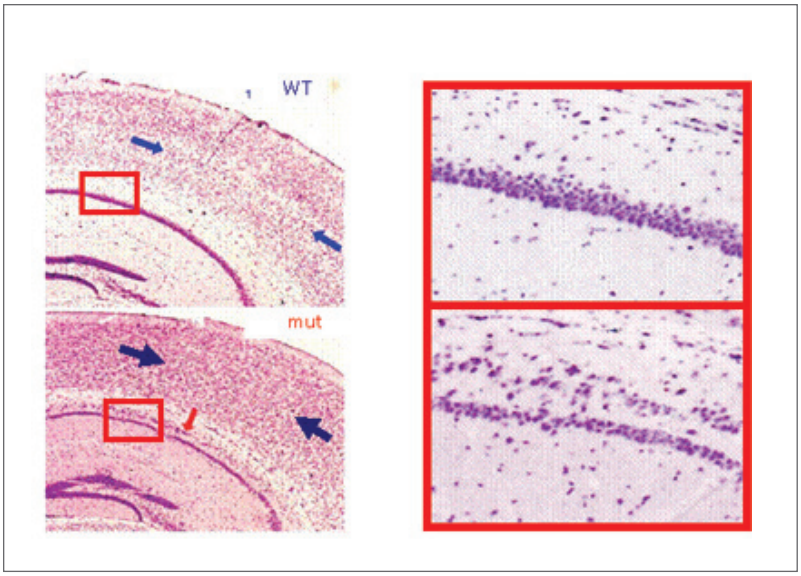

Figure 5: Symmetrical cortical and hippocampal lamination disturbances.[3]

Interestingly, about 30% of the mice with combined germline and somatic mutations also showed cortical and hippocampal lamination disturbances *(Figure 5)*. While the mechanism for it is unknown, we speculate that it may involve problems with generation of stem cells and or migration of neuroblasts during development.

Conclusion

Maternal inheritance of germline mtDNA mutations causes anticipation of reduced fertility, aggravates aging, shortens lifespan, and causes stochastic brain malformations when combined with somatic mtDNA mutations. Some recent studies in mice have shown the feasibility of mitochondrial gene therapy, and our studies support the importance of this approach for future therapy.

The authors report no financial relationships with commercial interests relevant to the content of this article.

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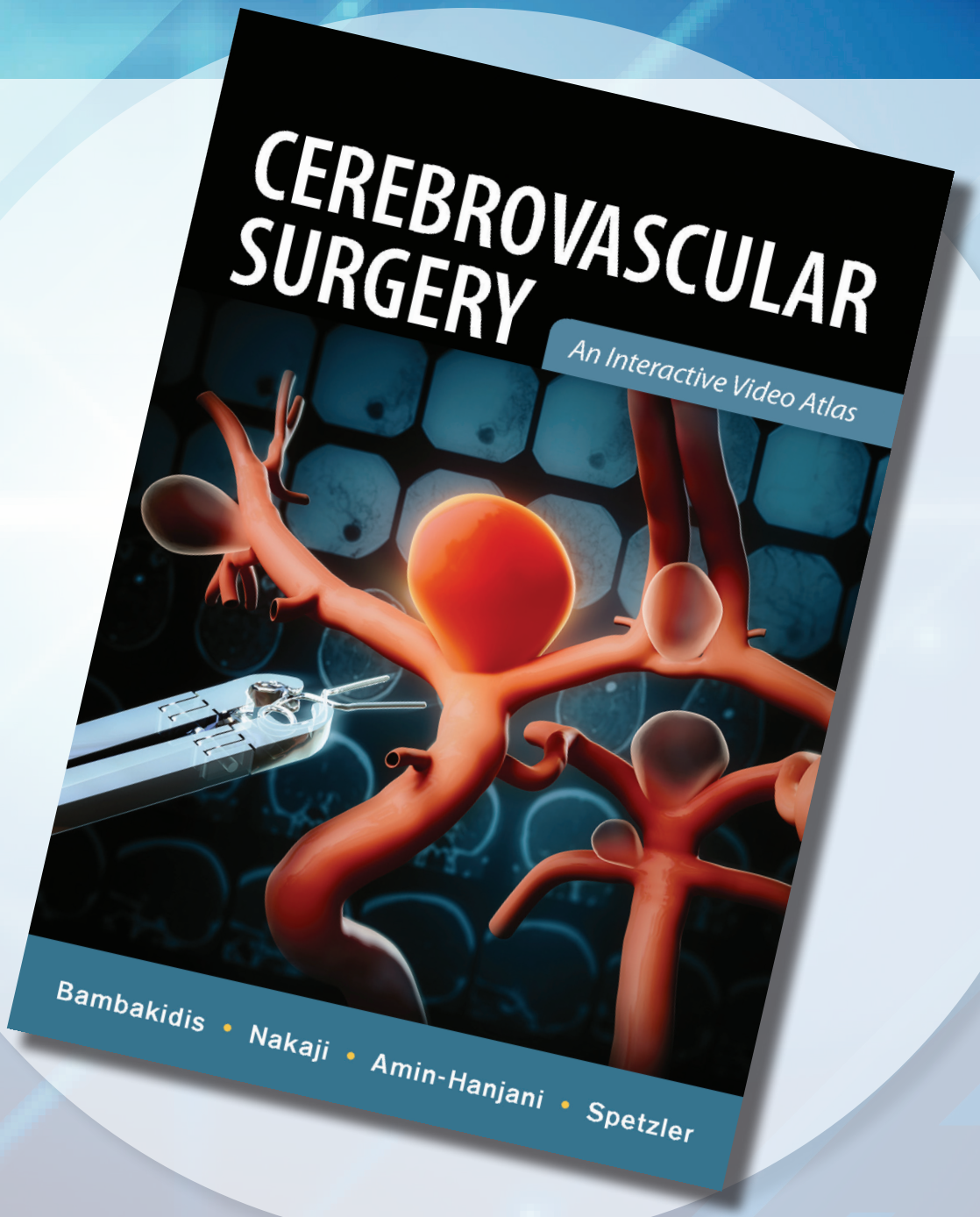
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