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Neurological Institute Journal

Inside:

- Interventional Therapies for Acute Ischemic Stroke
- Neurofibromatosis Type 2: Unraveling a Challenging Disorder
- Taking Brain Health to a Deeper and Broader Level
- New Developments in Tay-Sachs Disease

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Neurological Institute Journal

FROM THE EDITOR

Dear Colleague,

I am pleased to bring you the Spring 2010 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 NI Journal highlights these advances and demonstrates our interdisciplinary strengths. As an added benefit for our readers, CME credit is readily available in each issue for the busy practitioner interested in receiving *AMA PRA Category 1 Credits*™.

In our first issue of 2010, Shakeel Chowdhry, MD, and colleagues review interventional therapies for acute ischemic stroke. While these new therapies could become available to a greater number of patients, a quick response to stroke symptoms and access to a qualified medical team are essential for optimal treatment.

Maroun Semaan, MD, and colleagues consider the challenge of managing patients with neurofibromatosis type 2. Their article highlights recent advances in the genetics of the disorder, refinement in microsurgical techniques, and newer pharmacotherapeutic agents.

Peter Whitehouse, MD, PhD, takes brain health to a deeper and broader level in pursuit of holistic health for the betterment of ourselves, our community, and the world. He explores emerging brain health programs at University Hospitals and the surrounding community.

Finally, Barbara Shapiro, MD, PhD, describes the latest therapeutic techniques for managing Tay-Sachs disease. Her article gives special attention to what the future may hold for treatment of this degenerative lysosomal disorder.

The NI Journal requires the time and effort of many talented individuals who strive to make each issue a valuable contribution to patient care and neuroscience. Your suggestions and comments are always welcome.

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The commitment to exceptional patient care begins with revolutionary discovery. University Hospitals Case Medical Center is the primary affiliate of Case Western Reserve University School of Medicine, a national leader in medical research and education and consistently ranked among the top research medical schools in the country by U.S.News & World Report. Through their faculty appointments at the Case Western Reserve University School of Medicine, physicians at UH Case Medical Center are advancing medical care through innovative research and discovery that bring the latest treatment options to patients.

On the cover: *A middle cerebral artery clot being removed by a Penumbra device and an endovascular stent at the origin of the internal carotid artery. Read more about this case in the article by Shakeel Chowdhry and colleagues on page 2. (Illustration by Ravin Art & Design.)*

Kim Duvall, *Editorial Manager*
Heather Sandrey, *Senior Graphic Designer*

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University Hospitals Neurological Institute

University Hospitals Neurological Institute is Northeast Ohio's first designated institute for the comprehensive care of patients with diseases affecting the nervous system. The institute comprises 16 Centers of Excellence, which bring together some of the country's foremost experts in neurology, neurosurgery, neuroradiology, neuro-oncology, neuro-ophthalmology, neurotology, neuropathology, neuropsychology, neuropsychiatry and related specialties.

The UH Neurological Institute offers an interdisciplinary approach to highly individualized therapies and offers leading-edge care, including stereotactic radiosurgery, endovascular stroke and aneurysm treatments, neurostimulation and artificial disc replacement.

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Interventional Therapies for Acute Ischemic Stroke

By
Shakeel A. Chowdhry, MD
Cathy A. Sila, MD
Kristine Blackham, MD

Stroke is the third leading cause of death in the United States after cardiovascular disease and cancer.[1] Approximately 700,000 people suffer a stroke each year.[2] The vast majority – 87% or five out of every six – are ischemic strokes and result when a reduction in blood flow to part of the brain leads to irreversible injury or infarction. Stroke is a major public health concern. As one of the leading causes of long-term disability in the United States, it costs more than $62 billion in health care costs and lost productivity.[2] A stroke can injure any part of the brain by affecting any of the vessels that supply the brain parenchyma. The presenting signs and symptoms of stroke depend on the size and number of vessels affected as well as the part of the brain that those vessels perfuse (Figure 1). After suffering a stroke, more than one-half of people are able to regain functional independence, but 15-30% of people are permanently disabled, and about 20% require institutional care (Figure 2).

NIH Stroke Scale Item	Scoring Definition
1a. LOC	0 – alert and responsive 1 – arousable to minor stimulation 2 – arousable only to painful stimulation 3 – unarousable or only reflex response
1b. LOC questions	0 – both correct 1 – one correct, or unable to speak but not aphasic 2 – neither correct (aphasic, stuporous)
1c. Commands – Open/close eyes, Grip/release hand	0 – both correct, ok if weak 1 – one correct 2 – neither correct
2. Best gaze – Voluntary or Doll's	0 – normal 1 – partial gaze palsy 2 – forced deviation not overcome by Doll's
3. Visual field – To confront or threat, if monocular score one eye	0 – normal 1 – partial hemianopia, extinction 2 – complete hemianopia 3 – bilateral hemianopia or cortical blindness
4. Facial palsy	0 – normal 1 – asymmetric smile, NLF flattening 2 – partial paralysis of lower face (UMN) 3 – complete paralysis upper and lower face
5. Motor Arm – outstretched 90° sitting or 45° supine for 10 sec 5a – Left, 5b – Right	0 – no drift 1 – drift, doesn't hit bed 2 – some antigravity can't sustain 3 – not antigravity, falls to bed 4 – no movement at all
6. Motor Leg – outstretched 30° supine for 5 sec 6a – Left, 6b – Right	0 – no drift 1 – drift, doesn't hit bed 2 – some antigravity can't sustain 3 – not antigravity, falls to bed 4 – no movement at all
7. Limb ataxia – finger-nose-finger, heel shin, score only if out of proportion to weakness	0 – not ataxic or not testable 1 – ataxic in either arm or leg 2 – ataxic in arm and leg
8. Sensory – use pin, score if only stroke-related sensory loss, check grimace if stuporous.	0 – normal 1 – mild-mod loss but aware of being touched 2 – total or bilateral loss, unaware of touch, coma
9. Best Language – use cards, write if intubated	0 – normal 1 – mild-mod, can identify cards from responses 2 – severe – fragmentary, can't identify materials 3 – mute, global – no usable speech or comprehension
10. Dysarthria – use cards, untestable if intubated	0 – normal 1 – mild-mod slurs, can be understood 2 – severe; unintelligible, mute, anarthric
11. Extinction, Inattention – must have some unilateral function present for test	0 – no abnormality 1 – visual, tactile, auditory, spatial or personal inattention or extinction to DSS 2 – profound hemi-inattention, > 1 modality, denial of deficit

Figure 1: The National Institutes of Health (NIH) Stroke Scale is used to determine the severity of a stroke and track changes in a patient that presents with stroke-like symptoms. DSS = double simultaneous stimuli, LOC = level of consciousness, UMN = upper motor neuron

Modified Rankin Score

0 **No stroke symptoms** at all. (May have other complaints)

1 **No significant disability** despite persistent stroke symptoms. Able to carry out all usual duties and activities.

2 **Slight disability**. Unable to carry out usual activities, able to look after affairs without assistance, could live alone.

3 **Moderate disability.** Requiring some help but able to walk without assist (of a person), can be left alone for a few days.

4 **Moderate to severe disability**. Unable to walk without assist (of a person), unable to attend to own bodily needs without assist, could be left alone for a few hours of a day.

5 **Severe disability**. Bedridden, incontinent, and requiring constant nursing care and attention and 24 hr supervision.

6 **Dead**.

Figure 2: The Modified Rankin Score is used to summarize the functional capacity of a given patient.

Acute stroke care has evolved considerably over the past several decades and currently combines well-established medical therapies with endovascular therapies for select patients that meet strict criteria. As awareness of stroke symptoms improves, more patients could be eligible for these newer therapies; however, the majority of victims do not present for medical care within the time window for optimum therapy.

Reperfusion Strategies for Acute Ischemic Stroke: Intravenous Thrombolytic Therapy

Stroke is a dynamic process, and the recognition that brain tissue remains viable for a period of time led to a focus on therapies to restore blood flow so that symptoms could resolve as the affected parenchyma (or brain tissue) regained its function.

Following paths forged by cardiologists managing acute myocardial infarction, acute stroke therapy research employed thrombolytic agents or "clot busters," including the intravenous administration of the following: streptokinase, urokinase (UK), recombinant tissue plasminogen activator (rt-PA), recombinant prourokinase (r-proUK), and retaplase. These medications differ slightly in their half-life, fibrin selectivity, stability, and mechanism of action.

Eight large multicenter trials of intravenous thrombolysis were conducted over the past three decades. The first three trials (Multicenter Acute Stroke Trial – Europe, Australian Streptokinase Trial, and Multicenter Acute Stroke Trial – Italy) were stopped due to the high rate of intracerebral hemorrhage (ICH) and death and failed to demonstrate benefit within four to six hours of stroke symptom onset. Subsequently, the European Cooperative Acute Stroke Study (ECASS) I & II and Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS) trials evaluated intravenous rt-PA within four to six hours of stroke onset. Although they, too, failed to show any benefit in the primary endpoint of neurological improvement at 90 days, they did suggest that under certain conditions the medication may be beneficial. These studies were pivotal in identifying a dosing range and treatment protocol as well as ideal candidates who might benefit from such therapy. Subsequently, the National Institutes of Neurologic Disorders and Stroke (NINDS) conducted trials to evaluate use of intravenous rt-PA within 90 minutes and within three hours of stroke symptom onset, and the positive results led to the Food and Drug Administration (FDA) approval in 1996 of the first therapy to treat patients with acute ischemic stroke. Stroke patients who received intravenous rt-PA were 30% more likely to have minimal or no disability at 90 days compared to those patients who received placebo. Although symptomatic intracerebral hemorrhage was higher for those who received intravenous rt-PA (6.4% vs. 0.6%), it did not translate into an increase in mortality. Subsequent studies focused on identifying patients who might also benefit outside the three-hour treatment restriction as intravenous thrombolysis was used in less than 5% of acute stroke patients, mostly because patients present too late to be eligible for the treatment.[3] In 2009, the ECASS III trial demonstrated that the same dosage of intravenous rt-PA could be given to a highly restricted patient population with improved outcomes when administered after three hours but within four-and-a-half hours of stroke symptom onset. The ECASS-III protocol of intravenous rt-PA administration within four-and-a-half hours has been adopted by all major stroke societies but is not FDA-approved.

STROKE AND CEREBROVASCULAR CENTER

Cathy A. Sila, MD
Director

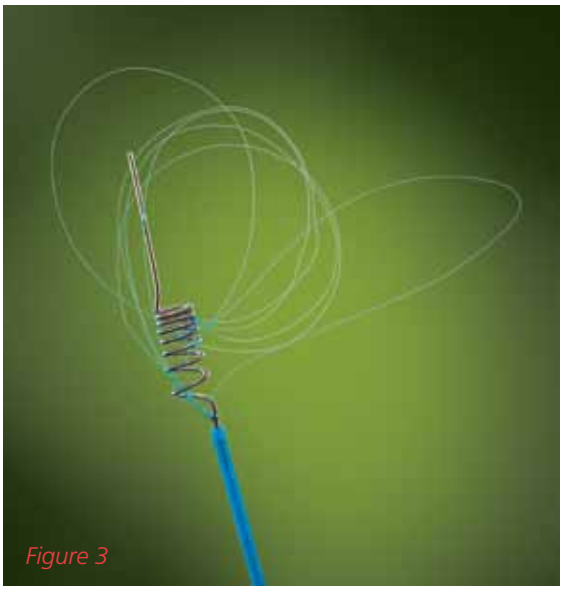
The Stroke and Cerebrovascular Center is the most experienced stroke center in Northeast Ohio. It comprises a world-class, multidisciplinary team including board-certified vascular neurologists, neurointensivists, interventional neuroradiologists, and cerebrovascular neurosurgeons. This team provides comprehensive diagnosis and treatment for patients with vascular disorders of the brain and spinal cord, including emergent evaluation of transient ischemic attacks and stroke, aneurysms, arteriovenous malformations, intracranial stenosis, stroke due to cardiac disease, cerebral vasculitis, and migraine. Clinical trials and translational research related to these disorders offer patients access to therapies not otherwise available or reimbursed by their insurance.

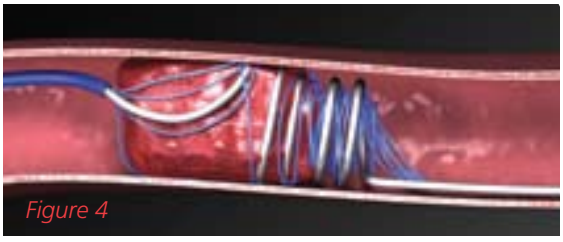
The Stroke and Cerebrovascular Center's collaboration with the Case Western Reserve University School of Medicine enables basic science research to be translated to findings that will improve future patient care.

Tailoring Treatment Directly to the Site of Blockage: Intra-arterial Thrombolysis

Intravenous thrombolytic therapy results were encouraging, but a good outcome was less likely in the setting of a major arterial occlusion. Although intravenous treatment could be accomplished with minimal infrastructure and equipment, some centers had good success with direct intra-arterial delivery of thrombolytic medication. Intra-arterial delivery allows for rapid local delivery of the medication with a greater concentration of thrombolytic agent at the site of the occlusion and lower concentrations systemically. This therapy was initially studied as an alternative to intravenous thrombolysis, particularly for patients that fell outside the treatment time window for intravenous rt-PA.

The Prolyse in Acute Cerebral Thromboembolism Clinical Trials I & II (PROACT I & II) focused on a more homogeneous population of stroke patients with an otherwise poor outcome (middle cerebral artery occlusion) and established the principle of intra-arterial thrombolysis in the management of ischemic stroke due to major intracranial occlusions and safety and efficacy of r-proUK.[4] Recanalization rates of up to 70% were reported for these large vessel occlusions with a significant increase in good neurological outcome. Like the intravenous studies, intracranial hemorrhage rates increased significantly but did not lead to a higher mortality rate. These studies as well as others supported the concept that early revascularization generally resulted in better clinical outcome (Table 1).





Figures 3 and 4: The Concentric MERCI retrieval device. The coiled loops are used to draw the occlusive clot out of the affected vessel. © 2010 Concentric Medical, Inc. All rights reserved.

If One Is Good, Then Two Must Be Better: The Synchronous Use of Intravenous and Intra-arterial Thrombolytic Therapy

Although intra-arterial thrombolytic therapy has a beneficial role, it requires that the patient be in an equipped facility with a trained endovascular specialist available. Additionally, there is an inevitable time delay as arterial access must be obtained and a catheter positioned proximal to the site of occlusion. Thus, studies were performed to evaluate combining intravenous and intra-arterial thrombolytic therapy. The Emergency Management of Stroke Bridging Trial performed in 1999 showed that combining the approaches resulted in more complete middle cerebral artery recanalization than intravenous therapy alone (55% vs. 10%), but failed to show a significant difference in clinical outcome.[5] In 2001, Keris and colleagues studied administration of intra-arterial thrombolytic therapy first and then randomized patients to either intravenous thrombolytic therapy or placebo.[6] A difference in intracerebral hemorrhage was noted, but no significant difference was seen in the rates of symptomatic intracerebral hemorrhage, mortality, or functional outcome (Table 2).

These studies were followed by the Interventional Management of Stroke (IMS) Trials. The combined intravenous and intra-arterial therapy approach was compared to matched NINDS trial patients who had received only intravenous rt-PA.[7] For 80 patients with a severe stroke (mean National Institutes of Health Stroke Scale [NIHSS] score of 18) who received intravenous rt-PA followed by a two-hour infusion of intra-arterial rt-PA, the three-month mortality was 16% and the symptomatic intracerebral hemorrhage rate was 64% (Figure 1). The patients in the IMS trial had significantly better outcomes at three months than the NINDS placebo group for all outcome measures performed in the study. A regression analysis of the hemorrhage rates compared to large clinical trials identified the proximal location of the blockage in a large vessel (e.g., internal carotid artery) and atrial fibrillation as independent risk factors for hemorrhage. IMS II continued as a larger follow-up trial to evaluate efficacy. Currently under enrollment is IMS III, which seeks to compare intravenous rt-PA alone or in combination with various forms of intra-arterial intervention, such as Mechanical Embolus Removal in Cerebral Ischemia (MERCI), EKOS ultrasound microinfusion catheter, or intra-arterial rt-PA.

PROACT II	Revascularization Rate	Symptomatic Hemorrhage	mRS score at 3 months
Control	18%	1.8%	25% - 0, 1, or 2
Intra-arterial Lytic	66%	10%	40% - 0, 1, or 2

mRS modified Rankin Scale

Table 1.

	All ICH	mRS score 0-3 at 1 month	mRS score at 12 months
IA followed by IV	17%	67%	83%
IA alone	6%	21%	33%

IA intra-arterial
IV intravenous
ICH intracerebral hemorrhage
mRS modified Rankin Scale

Table 2.

Other Medical Therapies Under Evaluation

Histopathological and physiological studies have shown that platelet aggregation is one of the first events to occur in the arterial thrombosis occlusion cascade. Thrombolytic therapy with rt-PA can paradoxically promote thrombus formation by stimulating plasmin production, thereby activating platelets. In the management of acute coronary occlusions, thrombolytic agents are typically combined with antithrombotic agents to prevent the aggregation of platelets. Monoclonal antibodies, like abciximab, inhibit platelet aggregation by binding to platelet fibrinogen receptor glycoprotein IIb/IIIa. Abciximab is useful in treating hyperacute intraprocedural thromboembolic complications during procedures such as vessel stenting or aneurysm coiling. Unfortunately, hemorrhagic transformation of the ischemic infarct is the limiting factor in acute stroke therapy. A single study of intra-arterial UK with and without abciximab showed a higher rate of recanalization when the monoclonal antibody was used in conjunction with the thrombolytic drug with a reduction in the dose of UK required. A trend toward improved outcome was noted, but statistical significance was not shown. Lee and colleagues[8] case series suggest an increased risk of symptomatic ICH when combined with mechanical clot disruption. This risk may be ameliorated with some of the shorter half-life drugs such as eptifibatide or tirofiban, but further studies are needed to evaluate the risks and benefits of adjunctive antiplatelet medications during endovascular reperfusion.

Era of Mechanical Thrombectomy

As described previously, restoration of flow to the ischemic penumbra or tissue at risk is the goal for acute stroke intervention. Direct removal of the clot from the vessel represents the newest FDA-approved treatment option for patients with stroke.

MERCI Device

The MERCI device (Concentric Medical, Inc., Mountain View, CA) is the first mechanical thrombectomy device approved by the FDA (approved 2004). The MERCI trials were performed in 25 hospitals and involved the use of a flexible, tapered, nitinol wire with five helical loops (Figure 3). These wire loops are embedded within the thrombus and allow for retrieval of the clot from the vessel (Figure 4). Inclusion criteria for phase I were as follows: NIHSS greater than eight, treatment within eight hours of onset of symptoms, angiogram demonstrating vessel occlusion, and ineligibility for intravenous rt-PA. Phase II included patients on anticoagulants with an international normalized ratio less than three (Table 3).

MERCI Trial
1809 patients screened, 151 enrolled, 141 treated with MERCI devices
48% recanalized to TIMI score 2-3
7.1% significant procedural complications
7.8% symptomatic intracerebral hemorrhage
44% mortality rate
27% good clinical outcome

MERCI Mechanical Embolus Removal in Cerebral Ischemia
TIMI thrombolysis in myocardial infarction score

Table 3.

Multi MERCI Trial
1088 patients screened, 177 enrolled, 164 treated with MERCI devices
68% recanalized (to TIMI score 2-3)
5.5% significant procedural complications
9.8% symptomatic intracerebral hemorrhage
34% mortality rate at 90 days
36% good clinical outcome

TIMI thrombolysis in myocardial infarction score

Table 4.

The MERCI trial did not have a control arm but used the spontaneous recanalization rate of 18% from the PROACT II trial as a baseline control. Patients with successful recanalization were more likely to score 0-2 on the modified Rankin Scale (mRS) at 90 days (46% vs. 10%) and lower mortality (32% vs. 54%) (Figure 1).

The Multi-MERCI trial was a multicenter, prospective, single-arm trial that included patients who received intravenous tissue plasminogen activator but had persistent arterial occlusion. There was no significant increase in ICH rate or procedure-related complications, thereby demonstrating that administration of intravenous rt-PA with adjuvant mechanical thrombectomy is safe. Also, successful recanalization was associated strongly with a good neurologic outcome (mRS 0-2 at 90 days, 49% vs. 10%) and lower mortality (25% vs. 52%) (Table 4).

These two trials suggest that the best results are achieved with combined mechanical thrombectomy and thrombolytic treatments. There are currently two ongoing trials involving the MERCI device. The MRI and Recanalization of Stroke Clots Using Embolectomy Trials is sponsored by the National Institutes of Health and seeks to determine if diffusion-perfusion magnetic resonance imaging prior to stroke intervention can identify patients who might benefit from mechanical embolectomy with MERCI. The IMS III trial also includes use of the MERCI device in one of its treatment arms and seeks to determine the efficacy of mechanical intervention over intravenous thrombolysis.

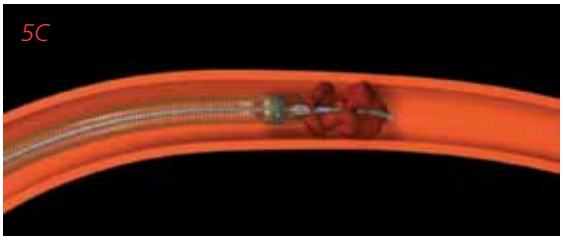


Figure 5: (A) The Penumbra reperfusion catheters and their corresponding separators. The catheters are available in numerous sizes. (B) The Penumbra reperfusion suction pump is connected to the Penumbra reperfusion catheter and provides continuous suction when activated. (C) Cartoon graphic demonstrating the Penumbra separator engaging a thrombus and drawing back to assist in suctioning the thrombus out of the body.

Penumbra System

The Penumbra System (Penumbra, Inc., Alameda, CA) is a new mechanical thrombectomy device, designed specifically to remove the thrombus in acute ischemic stroke secondary to large-vessel thromboembolism using aspiration, mechanical disruption, and extraction. It consists of four main parts: reperfusion catheter (four sizes: 0.054, 0.041, 0.032, 0.028 inches), separator, thrombus-removal ring (not approved for use in the United States), and vacuum pump (Figures 5A and 5B). Once the catheter is positioned proximal to the clot, the aspiration pump is connected to the catheter. The pump generates a vacuum of -20 inches of Hg, which reduces the clot burden. The separator is then advanced through the catheter into the distal clot, aiding the aspirating-debulking process (Figure 5C).

In 2008, Bose and colleagues published results demonstrating the efficacy of the Penumbra device in recanalization.[9] However, this study did not show improved neurologic outcome with greater recanalization rates, which may be due to the high baseline NIHSS scores on the patients enrolled (mean 21) and site of occlusion (9/21 with basilar artery occlusion). In 2009, a study by Kulcsar and colleagues[10] also evaluated Penumbra and suggested improved clinical outcome with lower NIHSS scores and revascularization rates. Kulcsar obtained a revascularization rate of 93% with complete revascularization in 52% of patients. The mean baseline NIHSS score was 14, 56% of patients had a four-point or greater decrease in NIHSS score prior to discharge, and 48% had a good neurologic outcome (mRS 0-2).

Other Interventional Therapies Under Evaluation

In addition to these FDA-approved interventions for acute ischemic stroke, several other modalities are currently being investigated, including stenting for acute and chronic occlusion, snares, and sonothrombolysis. (Stenting is currently performed routinely for patients with severe stenosis, or vessel narrowing, and stroke symptoms, as detailed in Case 2.) These modalities are studied at institutions such as University Hospitals Case Medical Center and, if proven effective and safe, will be incorporated into the armament of interventional therapies for stroke.

What is the Window for Treatment?

In most of the studies, the therapeutic window was defined as a specified time from stroke symptom onset with differing intervals for treatment that were often a compromise between what was physiologically reasonable and what was possible to accomplish. Advances in noninvasive imaging have allowed for improved identification of potentially viable ischemic tissue, or tissue at risk, from unsalvageable areas of infarction. This distinction is important. Infarcted

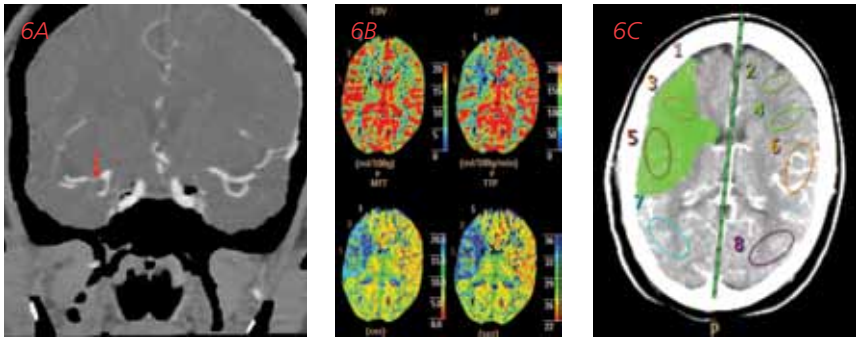


Figure 6: (A) Computed tomography (CT) angiogram. Coronal maximum intensity projections demonstrate an area of severe right M2 stenosis (arrow) in a patient with left-sided stroke symptoms that began more than six hours ago. (B) CT perfusion. Special contrast sequences can be obtained that evaluate the flow of blood in the brain tissue and the amount of blood in the brain tissue. CBF = cerebral blood flow, CBV = cerebral blood volume, MTT = mean transit time, P = posterior, TTP = time to peak. (C) An area of "perfusion mismatch," which identifies tissue with an insufficient blood supply that is still viable and salvageable.

tissue will not regain function. Moreover, the blood-brain barrier is compromised in areas of infarction. Restoring flow to areas of infarction can cause hemorrhage that may leave the patient much worse off than without any treatment. However, restoring flow to ischemic tissue improves the chances for that tissue to regain function and may lead to a decrease in the severity of the stroke. Imaging modalities, such as computed tomography (CT) perfusion, magnetic resonance perfusion, and Xenon CT scan, help to identify the "ischemic penumbra" and the "infarction core." Additionally, sites of large vessel occlusion can be seen on rapid noninvasive studies, such as CT angiograms, which can aid in the decision-making process for mechanical intervention (Figure 6).

The Current Management of a Patient with Stroke: Four Case Examples

The current management of acute stroke at UH involves the seamless and fluid coordination of numerous health care providers (Figure 7). Patients with stroke symptoms are evaluated and intravenous thrombolysis is initiated unless contraindicated. Patients are transferred to the main campus at UH Case Medical Center, and further noninvasive imaging is tailored to the patient's symptoms and presentation history to determine the ratio of the infarction core to the ischemic penumbra. Candidates with favorable profiles and clinical or radiographic evidence of vessel occlusion are then brought to the neuroangiography suite for intervention, which may include intra-arterial thrombolysis and mechanical embolectomy.

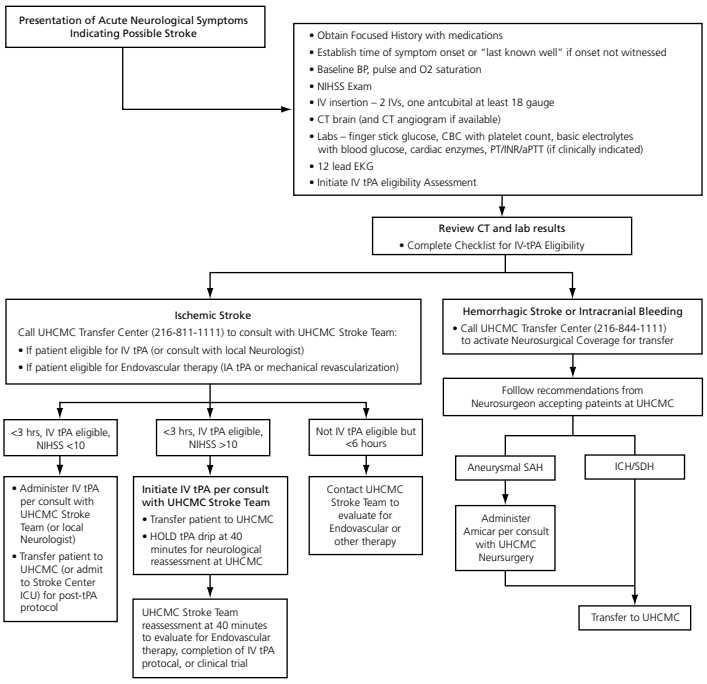


Figure 7: The acute stroke clinical practice guideline employed by University Hospitals. aPTT = activated partial thromboplastin time, BP = blood pressure, CBC = complete blood count, CT = computed tomography, EKG = electrocardiogram, IA = intra-arterial, ICH = intracerebral hemorrhage, ICU = intensive care unit, INR = international normalized ratio, IV = intravenous, NIHSS = National Institutes of Health Stroke Scale, 0_2 = oxygen, PT = prothrombin time, SAH = subarachnoid hemorrhage, SDH = subdural hematoma, tPA = tissue plasminogen activator, UHCMC = University Hospitals Case Medical Center.

Case I:

An 87-year-old man with hypertension, coronary artery disease, and congestive heart failure was noted to have left-sided fluctuating weakness on arrival to UH Case Medical Center. A magnetic resonance imaging with perfusion and time-of-flight angiography sequences revealed basilar artery narrowing with evidence of a completed stroke in a small portion of the pons (brainstem) and no perfusion deficits. He was initiated on intravenous rt-PA and noted to have an NIHSS score of 10. Following intravenous rt-PA, his exam was noted to worsen and he required intubation. He was taken to the angiography suite where a basilar artery occlusion was noted (Figure 8A). Intra-arterial rt-PA was employed (total 11.5 mg) with eight passes with the Penumbra System using various sizes. Successful recanalization of the basilar artery and the posterior cerebral arteries was achieved (Figure 8B). The patient's strength on his left side returned to baseline, and seven days later he was discharged to home with arrangements for home physical therapy. Note: Though not yet FDA-approved, intra-arterial rt-PA is undergoing clinical trials and has been successful for many patients.

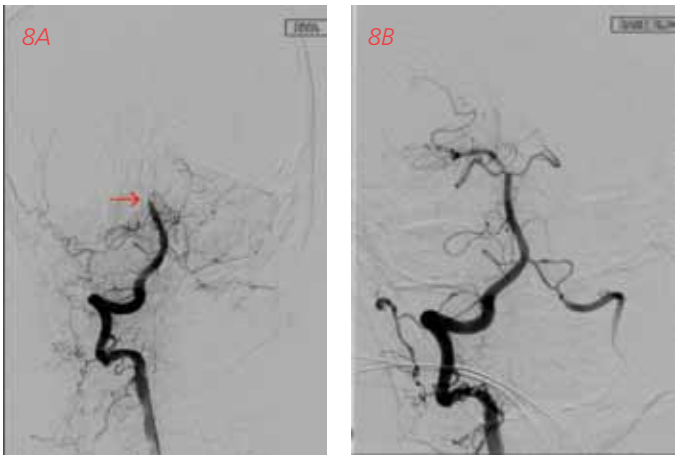


Figure 8: (A) Cerebral angiogram. Right vertebral artery injection demonstrating blockage at the distal aspect of the basilar artery (arrow). (B) Cerebral angiogram. Right vertebral artery injection following administration of intra-arterial rt-PA and use of the Penumbra reperfusion system with successful restoration of blood flow in the distal basilar artery and bilateral posterior cerebral arteries.

Case II:

An 80-year-old man with hypertension presented to an outside hospital with acute onset of right-sided severe weakness. A noncontrasted CT scan of the head demonstrated no evidence of hemorrhage. The patient's mental status began to decline. He was intubated, started on intravenous rt-PA, and taken to UH via helicopter. Upon arrival, he was taken immediately to the angiography suite. Imaging revealed severe left internal carotid artery stenosis (Figure 9A) for which a carotid stenting and angioplasty was performed (Figure 9B). Imaging of the head revealed blockage in a portion of the middle cerebral artery (Figure 9C) for which the Penumbra System was employed, providing significant improvement (Figure 9D). He was treated in the hospital for seven days and was discharged to home with an NIHSS score of two.

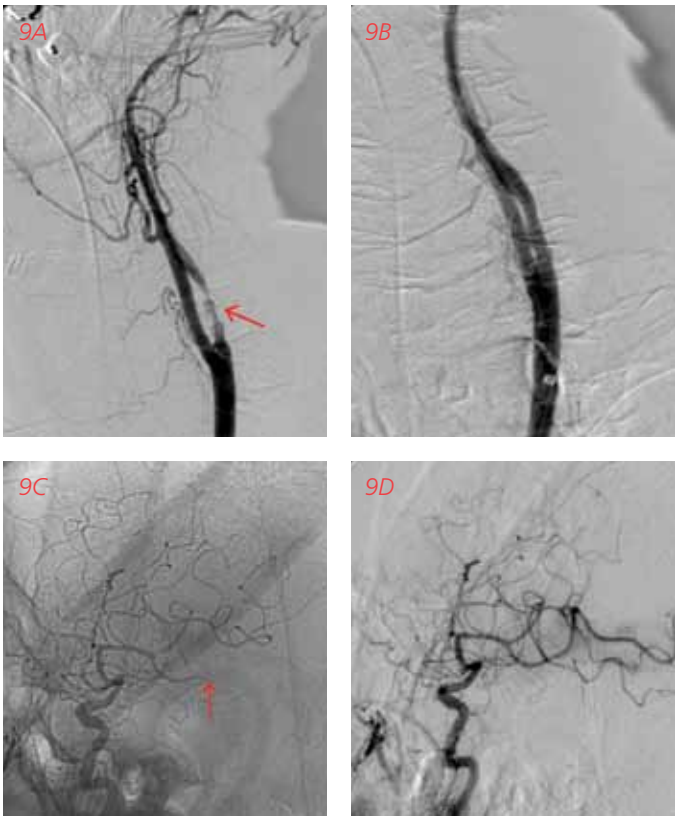


Figure 9: (A) Left common carotid injection with oblique views over the neck demonstrating left internal carotid artery stenosis (arrow). (B) Improved left internal carotid artery caliber and flow following stenting. (C) Lateral cerebral angiogram demonstrating blockage affecting vessel in the posterior middle cerebral artery distribution (arrow) with improvement (D) after use of the Penumbra reperfusion system.

Case III:

A 58-year-old right-handed man was found to have left hemiparesis shortly after waking in the morning. He was taken to an outside hospital and noted to have symptoms suggestive of a stroke. A noncontrasted CT scan of the head was performed and demonstrated no evidence of hemorrhage. The patient was started on intravenous rt-PA and transferred to UH via helicopter. He had a history of hypertension as well as deep vein thrombosis with pulmonary embolism for which he had been on coumadin for six months in 2008. His family history is significant for a cerebrovascular accident in his father. He was noted to have an NIHSS score of 20 on arrival at UH. He was taken immediately to the angiography suite where he was found to have a right carotid terminus occlusion (Figure 10A). Intra-arterial rt-PA was administered, and the Penumbra System was attempted resulting in minimal improvement. The patient was successfully recanalized after six passes with MERCI devices (Figures 10B and 10C). His neurologic exam improved considerably. After six days, he was discharged (NIHSS score of four) to a rehabilitation center for a two-week stay.

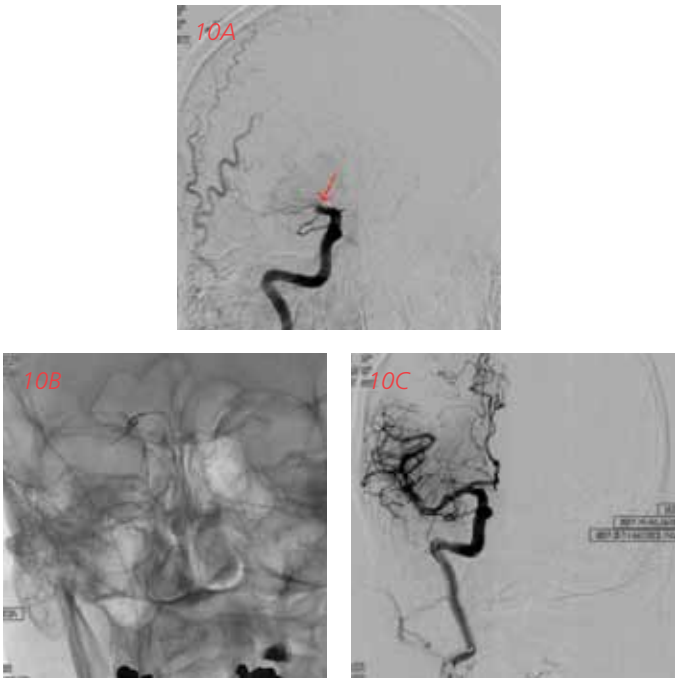
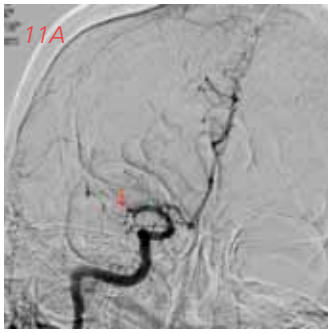
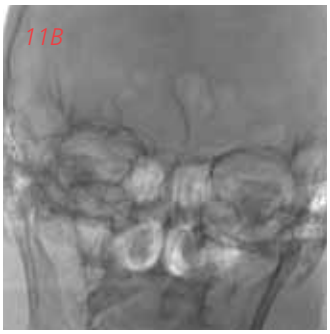


Figure 10: (A) Digitally subtracted cerebral angiogram demonstrating right carotid terminus occlusion (arrow). (B) Unsubstracted image showing the MERCI device in the site of blockage. (C) Final image demonstrating restoration of blood flow in the anterior cerebral artery and middle cerebral artery.

Case IV:

A 78-year-old right-handed woman collapsed at home after spending the morning shopping with her son. She had a past medical history significant for rheumatoid arthritis as well as right-hip and bilateral-knee replacements. She was admitted with dense left hemiparesis and an NIHSS score of 18. A noncontrasted CT scan of the head showed no hemorrhage. She was taken to the angiography suite and noted to have occlusion of the right middle cerebral artery (Figure 11A). A single pass with the MERCI device was performed (Figures 11B and 11C). Within hours of the procedure, the patient's NIHSS score improved to six.





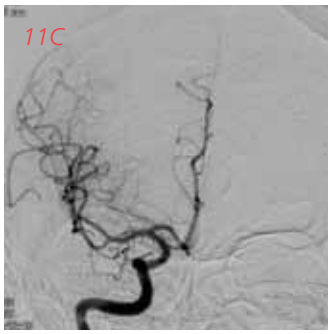


Figure 11: (A) Digitally subtracted cerebral angiogram revealing blockage in the distal right M1 segment of the middle cerebral artery (arrow). (B) Unsubstracted image showing the MERCI device in the site of blockage. The coils are deformed by the firm clot. (C) Final image demonstrating restoration of blood flow in the middle cerebral artery and its branches.

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Neurofibromatosis Type 2: Unraveling a Challenging Disorder

By
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Characterized by bilateral vestibular schwannomas (VS), neurofibromatosis type 2 (NF2) is an autosomal dominant disease that affects 1:33,000 to 1:40,000 live births.[1,2] In addition, patients with this condition present with central and peripheral nervous system schwannomatous and non-schwannomatous tumors (meningiomas, gliomas, and ependymomas) and cutaneous and ocular manifestations. Management of a patient with NF2 VS represents a considerable challenge and requires a multidisciplinary approach in specialized treatment centers. Tumor burden, a patient's hearing level, and other symptoms dictate an individualized treatment plan. Traditionally, large tumors with poor serviceable hearing were treated with microsurgery and hearing rehabilitation using an auditory brainstem implant (ABI).

The advent of gadolinium-enhanced magnetic resonance imaging (MRI) that allows detection of small intracanalicular tumors led some centers to adopt a proactive approach in patients with good serviceable hearing. The role of stereotactic radiotherapy (SRS) in the management of patients with VS in NF2 remains controversial. Recent advances in the genetics of NF2, refinement in microsurgical techniques and introduction of newer pharmacotherapeutic agents will be highlighted in this article.

Clinical Presentation

Bilateral vestibular schwannomas are pathognomonic for NF2. However, in 1991 the U.S. National Institute of Health Consensus Development Conference redefined the diagnostic criteria for NF2.[3] The diagnosis is made if a patient has (1) bilateral eighth cranial nerve masses on computed tomography or MRI, or (2) a first-degree relative with NF2 and either unilateral eighth cranial nerve vestibular schwannoma or one of the following in the family or patient: neurofibroma, meningioma, schwannoma, or juvenile posterior subcapsular lenticular opacities (Table 1).

Diagnosis of NF2

1. Bilateral eighth cranial nerve masses
   or
2. Family history of NF2 with
   - Unilateral vestibular schwannoma
   or
   - Glioma
   - Meningioma
   - Neurofibroma
   - Juvenile posterior subcapsular lenticular opacities

Table 1. Diagnostic criteria for neurofibromatosis type 2 (NF2) according to the National Institute of Health Consensus Development Conference (1991)

NF2 presents in the second and third decades of life and rarely in patients older than 60 years. In its more severe form, early onset in the first or second decades, an aggressive clinical course, and increased tumor burden are common. In the milder form, onset is typically delayed with a less aggressive clinical course. In addition to bilateral hearing impairment, the symptomatology varies greatly and is dependent on the degree of cranial nerve, dural, and spinal involvement.[4] Patients with optic nerve gliomas present with decreased visual acuity and eventual blindness. Involvement of cranial nerves III, IV, and VI results in diplopia and occulomotor dysfunction, and trigeminal nerve involvement causes facial hypesthesia and rarely trigeminal neuralgia. When the facial nerve is involved, facial paresis or paralysis may result. Bilateral hearing loss and progressive bilateral peripheral vestibulopathy may result from cranial nerve VIII involvement. Extensive involvement of cranial nerves IX, X, XI, and XII causes dysphagia, aspiration, dysphonia and atrophy of the hemitongue and suggests a poor prognosis. Large tumor burden leads to brainstem compression and development of obstructive hydrocephalus. Patients present with a worsening headache and visual disturbances and ultimately succumb to progressive tonsillar herniation if left untreated. Schwannomas, meningiomas, and ependymomas involving the spinal cord and peripheral nerves cause myelopathies or compressive sensory and motor neuropathies.

(Neurofibromatosis Type 2: Unraveling a Challenging Disorder continued)

NF2 belongs to the family of phacomatosis, combining neurological and cutaneous lesions. Café-au-lait spots and cutaneous neurofibromas can also be seen in patients with NF2, though in fewer numbers than seen in neurofibromatosis type 1. Juvenile posterior subcapsular lenticular opacities have been reported in 51% of patients with NF2. These are congenital lesions that offer the possibility of early screening in high-risk offspring or siblings. Retinal abnormalities have been described in the severe forms of NF2 and are usually indicative of a truncating genotype.

Unilateral VS in people younger than 30 years should raise the suspicion of NF2. In patients younger than 20 years, NF2 has been implicated in half the cases. Surveying other clinical signs (i.e., ophthalmological signs) helps to differentiate sporadic cases from NF2 cases.

Genetics

NF2 is a fully penetrant autosomal dominant disorder. Approximately 50% of affected patients will have an affected parent, indicating that de novo mutations in the NF2 gene account for a large proportion of nonfamilial cases. Once an individual has been diagnosed with classical NF2, his or her offspring has a 50% chance of inheriting the NF2 mutation and developing the disease. Whereas VS are the most common intracranial neoplasms involving the posterior fossa, accounting for 8% of all intracranial tumors, the majority appear to be sporadic. NF2 accounts for 3-5% of all VS.

Often confused with Von Recklinghausen's disease, also known as neurofibromatosis type 1 (NF1), NF2 is a distinct genetic and pathological entity (Online Mendelian Inheritance in Men #101000).[5] In 1987, genetic linkage analysis localized the NF2 gene to chromosome 22 and the NF1 gene to chromosome 17, confirming the genotypic-phenotypic difference between the two entities.[6,7] The NF2 gene encodes for a protein known as merlin (or schwannomin) resembling a family of proteins that includes ezrin, radixin, moesin, and members of the protein 4.1 superfamily.[8-10] These proteins are involved in linking the actin-rich areas of the plasma membrane to the cytoskeletal scaffold. In addition to maintaining cellular conformation and shape, these proteins play an important role in cell-cell and cell-matrix interaction. A loss of function of the merlin protein results in loss of contact inhibition and in cellular proliferation.

NF2 is classified as a tumor suppressor gene, with growth-inhibitory activity in the cell. Tumorigenesis involves a two-hit process[11] in which an inherited inactivating mutation in the NF2 gene is found in all constitutional cells. Benign tumors are thought to develop after a second mutation (second-hit) alters the remaining functioning gene, leading to cellular proliferation and tumor formation. Interestingly, haploinsufficiency, or the functional loss of one NF2 allele, has been associated with polyneuropathy in some patients with NF2. To date, more than 200 different mutations in the NF2 genes (single-base substitution, insertions, and deletions) have been identified. Depending on the type of mutation (truncating or nontruncating) the phenotypic expression varies.[12] A truncating mutation with complete or near-complete loss of protein function results in a more severe phenotypic expression, whereas a nontruncating mutation (missense or single-base substitution) results in a milder form of the disease. Maternally inherited genes appear to have a more severe expressivity with some elements of genetic anticipation.[2]

Segmental or mosaic categories of NF2 are common genotypic forms. In this subtype, somatic mosaicism results from a non-germline, post-zygotic NF2 mutation that occurs later during embryogenesis.[13] Therefore, only some of the somatic cells carry the mutation, and phenotypic expression tends to be milder and at times atypical (i.e., unilateral VS with multiple meningiomas) (Figure 1). This form is estimated to account for 25% of cases of NF2. Somatic, biallelic mutations in the NF2 gene have been described in sporadic VS, meningiomas, schwannomatosis, and tumors such as mesotheliomas,[14-16] indicating the importance of NF2 in growth control in benign intracranial neoplasms.

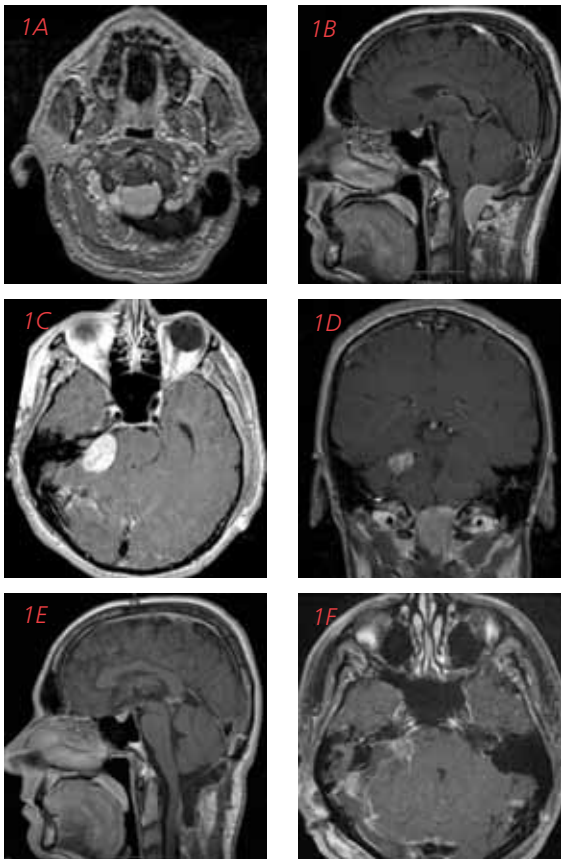


Figure 1: Magnetic resonance images of a 45-year-old man with the mosaic form of NF2. He presented with diminished hearing and the presence of a foramen magnum meningioma as well as a unilateral acoustic schwannoma (A, B, C, D). He was found to have multiple small spinal neurofibromas on further imaging (not shown). Both lesions were sequentially removed without morbidity (E, F). The acoustic tumor was removed via a retrosigmoid approach with successful preservation of residual hearing and normal cranial nerve function. Used with permission from Barrow Neurological Institute and PMPH-USA, Ltd.

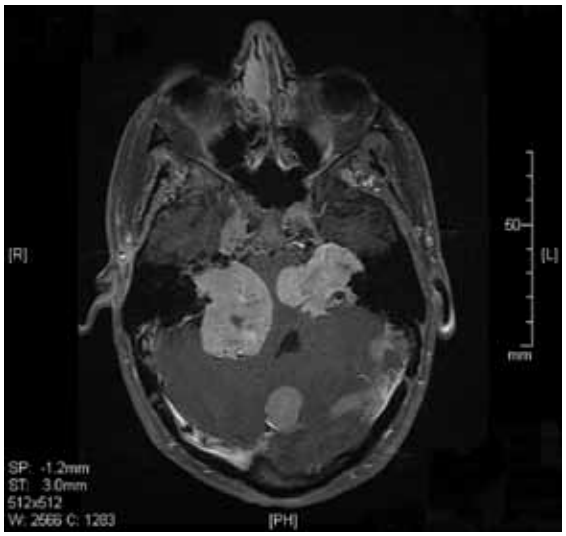


Figure 2: Gadolinium-enhanced MRI showing bilateral large vestibular schwannomas, a posterior fossa meningioma, and bilateral trigeminal nerve schwannomas.

CEREBROVASCULAR AND SKULL BASE SURGERY PROGRAM

Nicholas C. Bambakidis, MD
Director

The Skull Base Surgery Program provides a multidisciplinary team of specially trained and experienced surgeons to treat cerebrovascular and skull base disorders using minimally invasive, image-guided, and radiosurgical techniques. Specialists from neurosurgery, radiology, otolaryngology, ophthalmology, radiology, endocrinology, neurology, oncology, and radiation therapy have joined together to provide comprehensive care for complex clinical conditions, such as meningiomas, arteriovenous malformations, pituitary tumors, and acoustic neuromas. The skull base surgery team meets regularly to review new cases and determine the appropriate course of treatment for every patient. Each new case is discussed by members of the team, and care is tailored to the needs of the individual patient. Clinical and basic science research efforts are underway to advance the understanding of the cause, prevention, detection, and treatment of these diseases and disorders.

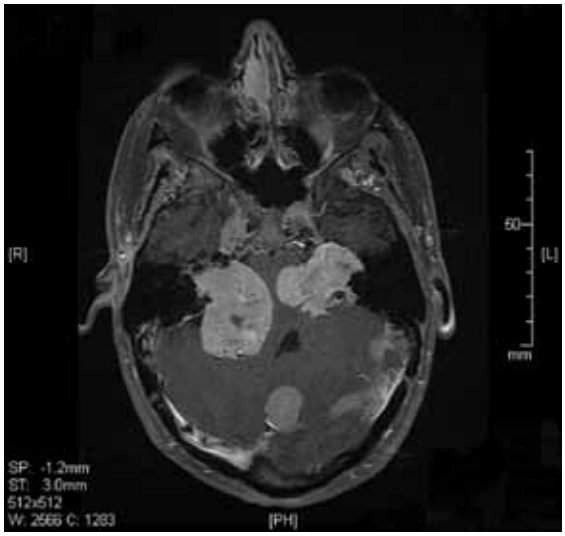


Figure 2: Gadolinium-enhanced MRI showing bilateral large vestibular schwannomas, a posterior fossa meningioma, and bilateral trigeminal nerve schwannomas.

(Neurofibromatosis Type 2: Unraveling a Challenging Disorder continued)

Diagnosis of VS and NF2

The introduction of genetic screening of at-risk family members and the paramagnetic agent gadolinium-pentetic acid (Magnevist, Berlex Laboratories Inc, Wayne, NJ) as a contrast agent for MRI revolutionized the management of NF2. Traditionally, patients were diagnosed with large bilateral tumors and poor serviceable hearing (Figure 2). The disruption of the blood-brain barrier membrane as evidenced by an increased uptake of gadolinium enables detection of tumors as small as 2 mm. Contrast-enhanced MRI is the gold-standard diagnostic modality. Patients suspected of having NF2 should undergo an initial brain and spinal MRI with contrast and at annual or semi-annual intervals thereafter. Current imaging allows detection of small bilateral VS in asymptomatic patients as part of a screening strategy in offspring or siblings of affected individuals. In addition to its diagnostic value, this early detection has potential therapeutic implications that will be discussed. Though rare, an MRI can be falsely positive. Viral cranial mononeuritis or polyneuritis can cause post-contrast enhancement of the affected nerve(s). Post-neuritic enhancement tends to be linear and nonglobular. In very small tumors, a repeat MRI in a few months is recommended to ascertain the diagnosis. Genetic screening is available in certain medical and specialized laboratory centers. Blood is drawn from affected family members, and genetic linkage analysis allows identification of the specific mutation, allowing genetic screening of asymptomatic members in the family. It is recommended that affected individuals undergo a yearly contrast-enhanced MRI beginning in their early teen years.

Treatment strategies for VS and NF2

The management of NF2 patients is complex and requires a multidisciplinary approach and an experienced team of health professionals.[17] Few centralized and specialized centers have the patient volume and the resources needed. In patients with newly diagnosed NF2, it is the clinician's responsibility to screen high-risk family members. Genetic screening, ophthalmologic examination, and gadolinium-enhanced MRI capture most affected individuals (Figure 3).

For VS or NF2, the variable tumor growth pattern, tumor burden, and clinical symptomatology dictate an individualized approach. In addition to tumor control or excision, hearing rehabilitative options should be considered.

Recently, bevacizumab (Avastin, Genetech, Inc), a monoclonal anti-vascular endothelial growth factor (anti-VEGF) receptor has been introduced in the treatment of a subset of NF2 patients considered not to be appropriate surgical candidates.[18]

Several treatment strategies exist:

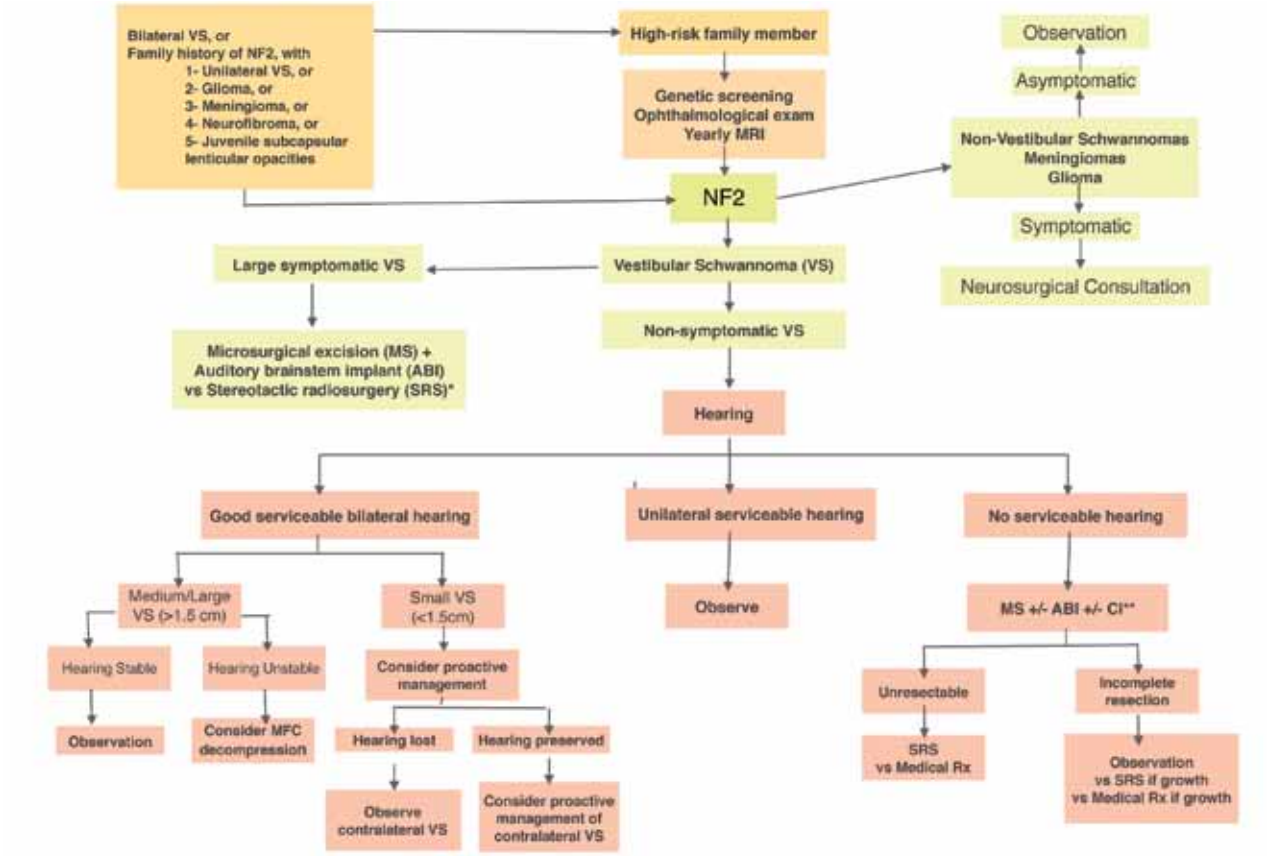
- Observation without surgical intervention
- Middle fossa decompression of the internal auditory canal without tumor removal
- Hearing preservation surgery with total tumor removal via a middle fossa approach or retrosigmoid craniotomy
- Hearing preservation surgery with partial tumor removal via a retrosigmoid approach
- Nonhearing preservation surgery with total tumor removal via the translabyrinthine craniotomy without auditory brainstem implant
- Nonhearing preservation surgery with total tumor removal via the translabyrinthine craniotomy with auditory brainstem implant

Tumor management

In patients with minimal to moderate VS tumor burden and absence of brainstem compression, preservation of hearing is paramount. Most patients will eventually be deafened by tumor growth or iatrogenically by nonhearing preservation or failed hearing preservation modalities. Criteria for hearing preservation are less stringent in NF2 than sporadic VS. The 50/50 rule (pure tone average worse than 50 dB or word-discrimination score worse than 50%) does not need to apply. As long as the patient is serviced by his residual hearing, preservation of hearing should be attempted. The "wait and see" approach (observation without surgical treatment) seems reasonable in patients with tumors that are not amenable to hearing preservation surgery. These patients should not have large tumors with significant brainstem compression. When contemplating a hearing preservation surgery, several prognostic factors have been described that favorably or unfavorably alter the hearing outcome. Poor preoperative hearing status, abnormal auditory evoked brainstem responses, abnormal vestibular evoked potentials, tumors larger than 2 cm, and the lateral location of the tumor carry a poor prognosis for hearing preservation.[19]

However, early detection of a small intracanalicular tumor led some centers to adopt a proactive approach with hearing preservation surgery via the middle fossa craniotomy or retrosigmoid approach in selected cases.[20-22] For unilateral tumors, a length of 1.5 cm is considered the upper limit to attempt hearing preservation surgery via the middle fossa craniotomy and 2 cm via the retrosigmoid approach. Hearing preservation in patients with NF2 has been reported to be worse than in sporadic cases.[23] The biological invasiveness of cochlear nerve infiltration or possibly apparent invasiveness due to the polyclonal origin in the vestibular nerve may explain this observation. A hearing preservation rate as great as 65% with 48% maintaining hearing within 15 dB or 15% of preoperative values has been reported.[21] In patients with hearing fluctuations and large tumors not

Figure 3: Suggested management algorithm. ABI: auditory brainstem implant; CI: cochlear implant; MRI: magnetic resonance imaging; MS: microsurgery; NF2: neurofibromatosis type 2; Rx: therapy; SRS: stereotactic radiotherapy; VS: vestibular schwannoma.



* use of SRS in the treatment of NF2 patients is controversial

** Cochlear implantation is possible in a subset of patients with intact and functional cochlear nerve. A promontory stimulation test (not required) confirms viability of spiral ganglia fibers.

Figure 4: Multichannel auditory brainstem implant. Image courtesy of Cochlear™ Americas, © 2009, Cochlear Americas

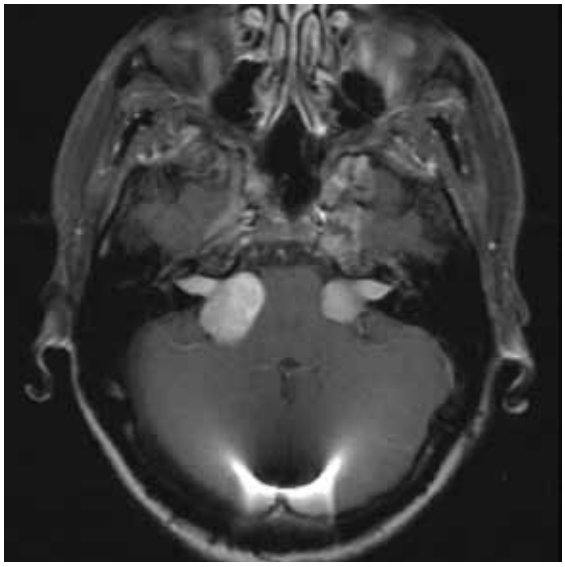


Figure 5: Gadolinium-enhanced axial magnetic resonance images of 30-year-old female showing large bilateral vestibular schwannomas prior to bevacizumab therapy.

amenable to hearing preservation, some surgeons advocate a middle fossa decompression of the internal auditory canal with dural incision, with no attempt at tumor debulking. This approach results in hearing stabilization and rarely improvement.[24] Partial tumor removal has been recommended by some surgeons to debulk a large symptomatic tumor, with an attempt to preserve residual hearing by leaving the tumor capsule on the cochlear and facial nerves. Though logical, this approach often results in hearing loss and rapid tumor growth.[25] In large symptomatic tumors with poor residual hearing, complete excision via the translabyrinthine approach is the treatment of choice. This approach allows a wide exposure of the cerebellopontine angle and the lateral recess. Extensive intralabyrinthine extension or concomitant intralabyrinthine schwannomas can be removed via a transcochlear approach. In NF2 patients, the advantage of the translabyrinthine approach is that it allows insertion of the ABI surface electrode array into the lateral recess.

The role of SRS is more controversial than surgical approaches. Rowe and colleagues[26] treated 122 VS in 92 patients with NF2. Eight years following treatment, tumor control was achieved in 50% of patients, though further treatment was required in 20% of patients, and there were concerns about tumor control in 30% of patients, who continue to be managed conservatively. Hearing was preserved in 40%, hearing deteriorated in another 40%, and 20% of patients became deaf following SRS. The high mutagenic potential observed in NF2 patients also raises concerns of an increased rate of malignant degeneration following SRS.[27-29] Though some centers continue to treat NF2 patients with SRS, others are more conservative.[30,31]

Recently, Plotkin and colleagues[18] reported treatment results with an anti-VEGF monoclonal antibody, bevacizumab (Avastin) in 10 patients with NF2. These patients had progressive VS that were not appropriate for surgical treatment. In nine patients the tumor shrank, and in six the tumor decreased in size more than 20% from baseline. This response was maintained in four patients for up to 16 months. In the seven patients with serviceable hearing at baseline, four had improvement in hearing and two were unchanged. The use of this drug remains restricted to specialized centers. The patient should be informed of the potential for adverse events associated with this drug.

Non-schwannomatous and non-vestibular schwannomatous tumors, when symptomatic, require an individualized approach. Generally, the most symptomatic or life-threatening tumor is treated and asymptomatic tumors are managed with a conservative approach.

Hearing rehabilitation

In anticipation of eventual deafness, patients with NF2 should be taught both verbal and non-verbal communication skills to enhance their speech reading and signing abilities. Two hearing rehabilitative options also exist: ABI (Figure 4) and cochlear implants.

In 1979, Drs. House and Hitselberger implanted the first ABI in a patient with NF2.[32] Currently, ABIs are approved by the Food and Drug Administration for patients with NF2 undergoing a translabyrinthine VS tumor removal who have (1) non-aidable hearing or an only-hearing ear with a symptomatic tumor or (2) serviceable contralateral hearing with a large tumor. Recipients should be 15 years of age or older and have evidence of a bilateral eighth cranial nerve tumor, competency in the English language, realistic expectations, a good social support, and a likeliness to comply with follow-up protocol.

The device has a surface electrode array that is placed in the lateral recess of the fourth ventricle to electrically stimulate the cochlear nucleus at the brainstem. An external processor with a transcutaneous coil system communicates with an electromagnetic internal receiver similar to multichannel cochlear implants. Intraoperative electrically evoked auditory brainstem responses (EABR) confirm electrode positioning and assess for unwanted nonauditory stimulation.

Most recipients are able to use auditory sensations to supplement lip-reading and visual cues. The majority of patients are device users (80%) with 16% of patients achieving open-set speech discrimination. This auditory ability is markedly enhanced when auditory-only cues are combined with visual cues (30 to 70%).[33,34]

In an effort to enhance the precision of brainstem auditory stimulation and minimize cross-stimulation of nonauditory neurons, a modified electrode array was designed by the House Ear Institute (Los Angeles, CA), the Huntington Medical Research Institutes (Pasadena, CA), and the Cochlear Corporation (Englewood, CO). This modification includes the addition of a separate array with penetrating electrodes, with the idea that microstimulation of the tonotopically organized cochlear nucleus will improve speech perception. A recent trial using a penetrating auditory brainstem implant in 10 patients with NF2 showed lower stimulation thresholds and higher pitch range and selectivity but failed to show improvement in the speech recognition score compared to surface electrodes alone.[35]

Multichannel cochlear implants have also been used in selective patients with good hearing outcome.[36,37] In deaf patients with an intact cochlear nerve (hearing preserving, nonpreserving surgery for a small VS or a subtotal excision or a larger VS), cochlear implantation can be offered. In larger tumors completely excised, the integrity of the nerve fibers has been violated and the cochlear nerve is rendered nonfunctional. A translabyrinthine craniotomy does not preclude implantation given that the cochlea remains intact.[38] Though not a prerequisite, EABR via promontory stimulation suggests viable spiral ganglia and may predict successful implantation.[37]

Conclusion

Generally considered to be an inherited disorder, NF2 requires complex multidisciplinary management. Family members at risk should be screened early. Symptoms and treatment modality varies depending on tumor load. An individualized treatment plan is usually the rule. Hearing restoration can be successfully obtained with ABI and cochlear implants in selected individuals.

Clinical Vignette

A 30-year-old female with a long history of NF2 recently transferred her care to UH. She has had 11 tumors identified and recently demonstrated declining hearing bilaterally associated with a 2 cm or larger growing bilateral acoustic neuroma (Figure 5). By virtue of the size of the tumor that rendered the success of hearing preservation removal surgery less than favorable, she elected to proceed with Avastin therapy in hopes of causing tumor growth cessation and hearing preservation. She has been on Avastin therapy for four months and her hearing is stable with minimal side effects of chemotherapy. A follow-up MRI revealed stability of her tumor. Genetic testing identified a pathologic NF2 mutation, which allowed for analysis of at-risk family members. Her 2-year-old daughter was subsequently found to carry the familial NF2 mutation. Though free of tumors via surveillance MRI, she is closely being followed by the team.

Nicholas C. Bambakidis, MD, is a consultant for Medtronic Sofamor Danek, though this relationship has not affected the content of this article. Cliff A. Megerian, MD, is a consultant for the Surgeon's Advisory Board, Cochlear Corporation, though this relationship has not affected the content of this article. Lisa R. Rogers, DO, is a speaker for Enzon Pharmaceuticals, Inc., though this relationship has not affected the content of this article. The other authors report no financial relationships with commercial interests relevant to the content of this article.

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Taking Brain Health to a Deeper and Broader Level

By
Peter Whitehouse, MD, PhD

Of the many people who sell brain health potions or programs, most have it wrong or at least incomplete. Considered in isolation, the concept of brain health is not really that important, but embedded in an integrative program of health, it becomes an essential component of a life plan. Most people are not actually concerned about the health of their organs individually. In fact, organ-specific health is a counterintuitive term since "health" derives from the Old English word for wholeness. When it comes to the brain, most people are more concerned about the quality of their thoughts and emotions (i.e., the products of the brain rather than the brain itself as a three-pound gelatinous mass of energized nerve cells). We should be aiming for total-body as well as total-mind health. New findings of modern science support the infrequently acted on but common sense notion that taking care of your entire body will result in a healthier brain and improved abilities to think, feel, and act. Yet even total body health is not a deep and broad enough concept to encompass brain health for the future. We must determine what we need to be holistically healthy and how to succeed on this journey toward integrated health.

In this article, we describe new programs emerging at University Hospitals Neurological Institute in collaboration with the community that take brain health to deeper and broader levels using a holistic approach. Any specific approach that works for an individual to enhance health in isolation is salutary but, in our view, an integrative approach is preferable.

What is health?

So what do we mean by health itself? The World Health Organization defines health as not merely the absence of disease but as a state of complete physical, mental, and social well-being.[1] In other words, a comprehensive view of health includes biological and psychosocial factors. Pills and procedures are not the only answer to staying well. Though staying healthy involves having access to good health care, other factors are equally important, if not more important. Those factors include one's self-efficacy for health matters and living in a community that supports wellness in a sustainable way.

A person's or a community's adaptability or resilience also affects their wellness.[2] Particularly in today's tumultuous times with physical (climate change and weather weirding) and mental forces (deep recessions and job insecurity) that are unbalancing our individual and community lives, it is important to be able to respond to change and stress to remain healthy. As the principal organ of learning, the brain plays a critical role in our ability to adapt. Our own aging will be a more successful, productive, and positive process if we maintain our resilience.

What is brain health?

The brain is embedded in the system of interdependent organs, and keeping the entire system healthy is the best approach to living well. However, the brain plays a particularly important role as the organ that learns and allows its owner to think and act in the world. Hence, the essential manifestation of brain health is mental health. Here, we mean mental health not just in the sense of the absence of psychiatric disease but rather supporting the ability of our brain to maintain its role in managing and enhancing our lives. Therefore, we must maintain cognitive health by keeping the brain engaged in activities that are both enjoyable and productive. Much discussion is given to the nature of the "best" brain health

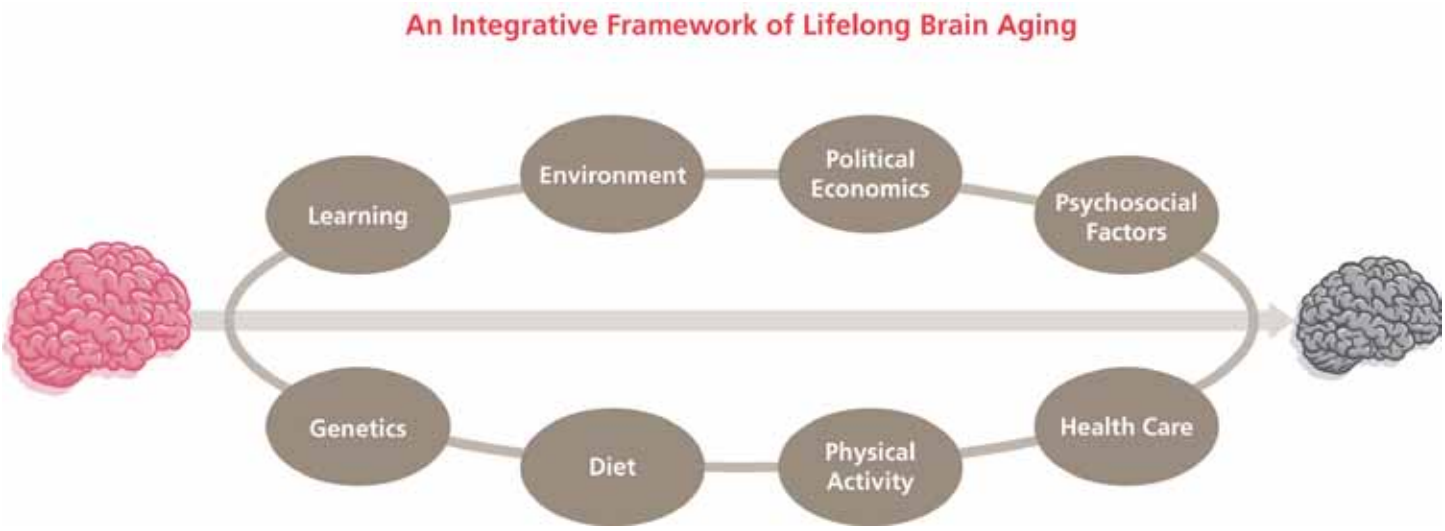

Figure 1: Life-span multicomponent model of brain health designed by Danny George and Peter Whitehouse

activities, and the data are sparse.[3] Many people are trying to sell computer programs that exercise specific parts of our mental apparatus. Our view is that these programs may be helpful for those who enjoy them, but a more comprehensive view of enhancing cognition would include participating in multifaceted lifelong learning activities, particularly those that involve other people.[4] Using the mind in social situations, particularly helping others, contributes to emotional well-being.[5,6]

Furthermore, the brain is about feeling and not just thinking. Being (brain) healthy means having a set of values that guides us to appropriate ethical behavior in our own lives and in the lives of others. All of us should be more attentive to the aspects of life that challenge our honesty and sense of integrity. Do we pay our taxes and support a just society, or do we look for every opportunity to benefit only ourselves? How much does the consumption and possession of material goods dominate our lives? Having well-reasoned and ethically sound positions on social issues will contribute to a healthier way of interacting with the world.

Some would consider these emotional and cognitive aspects of brain health linked to a superordinate category as spiritual health. For some, spiritual health is found in traditional religious forms of worship and, for others, in more secular though deep connections to other living creatures and nature itself. Regardless of one's religious beliefs, this dimension has been demonstrated to be important to mental health. Though notoriously difficult to articulate, the most generally humanistic way to do so is to say that everyone needs a reason to want to keep healthy. What is one's purpose in life?[7] Answering this question can be particularly challenging for elders, in a world where so-called retirement is being reconceptualized and having multiple encore careers is becoming more common. Indeed, one might say that the whole concept of aging is being reinvented to reflect life-span perspectives. When do we start the aging process? Certainly, it doesn't begin at 65 or even 85. Does it begin at birth or maybe in utero (Figure 1)?

Perhaps the most perverse attempt to reframe aging is by considering it as disease. "Cure aging and live forever" is the line of anti-aging proponents who sell their approaches to ridding one of the "disease" of aging. Whether it be human growth hormone and its analogues or some reptilian-related ointment, one needs to watch one's pocketbook carefully when dealing with these facile vendors of false vitality.

These approaches are built on fear – the fear of growing old and dying. A program of brain health needs to challenge dominant perspectives that affect our brain aging. For example, we consider the dominant model of Alzheimer's disease to be a myth.[8] Most experts do not believe Alzheimer's disease is a single condition, and many believe the brain aging processes we lump together as Alzheimer's disease are intimately related to aging. Hence, creating a program of brain aging becomes a way of preventing dementia. Moreover, it challenges ideas that Alzheimer's disease can be cured by simplistic notions of drug therapy.

However, our pro-aging attitudes require attention to biology. Here, we find increasing evidence that regular exercise is helpful to brain function. As one aspect of biological health, an exercise program can take many forms, but it should take a form that is enjoyable to the individual (and to groups of individuals) and allows one to accomplish a program of physical activity. Those who find exercising in nature with other people to be enjoyable, for example, are more likely to maintain a program if it includes nature and other people.

The other aspect of biological health is nutrition. Many claims are made that nutritional formulations ranging from antioxidants to anti-inflammatory agents, vitamins, and other potions help brain health. Most evidence suggests that eating a healthy, balanced diet composed predominantly of fruits and vegetables and free of pesticides and other toxins is probably the best way to maintain brain health through nutrition. Some recommend a Mediterranean type of diet with predominantly white meat like chicken and fish and healthy fats like those from olive oil. Eating low on the food chain (or following a vegetarian diet) and avoiding excessive or perhaps any red meat seems ideal from both a health and an ecological perspective. Sometimes vitamin supplements may be necessary, but naturally occurring sources of these metabolic constituents are probably ecologically and nutritionally best.

What Should Brain Health Really Be and Become?

Following the advice to maintain mental and physical health is an important aspect of brain health (Table 1). However, the brain serves many functions, not the least of which is to guide our lives down a journey of purpose.[7] Why do we want to be healthy? Why do we want our brains to work well? Presumably, it is because we have things we wish to accomplish in life.

This exploration of our purpose is perhaps the deepest layer of brain health. The most complex parts of the human brain are the frontal lobes and related regions that perform the so-called executive functions. All human beings need to have a set of goals and a plan to achieve those goals combined with a process to monitor progress toward their objectives. Paying attention to issues that are core to one's life and avoiding unnecessary distractions are key components of brain health. Relaxation techniques, mindfulness, and meditation can assist this process as can guided imagery, which uses the imagination to visualize positive outcomes. Likewise, positive psychology concepts stress that focusing on strengths and affirming emotions is essential for enjoying a productive life. Another essential approach is narrative medicine, which recognizes that patients' histories are key to not only diagnosis but treatment. For many, it is one's life story that provides coherence and connection to others. Stories recount our past as we tell them in the present while wondering how to act in a way that creates our healthy future.

Executive functions are broad. Will, purpose, and meaning are associated with this set of complex human abilities. Importantly, the frontal lobe is intimately connected to portions of the brain that regulate emotions. These are some of the older parts of the brain that we share with our fellow animals. In a sense, the frontal lobe with its interconnected parts is the organ of wisdom that "decides" how to balance our motivations with our plan of action. It is simplistic to say that wisdom is located in any particular part of the brain and, in fact, one would be better served speaking of an embodied mind since our bodies, through hormones and other metabolic systems, can dramatically affect our thoughts and emotions. Another component of wisdom is to recognize the limitations of human thought since humility is a key aspect of wisdom. So, too, is compassion for self and others. The embodiment of brain reminds us to pursue the health of the entire body.

A Deeper Notion of Brain Health

We claim that our brain health initiatives and health practices should focus on the profound aspects that link the components of brain health by finding purpose and goals for our lives. This shift represents a deeper notion of brain health, with a holistic concept of what it means to be a healthy human being, and liberates us from a sole focus on the neurons and synapses that comprise our brains. It also has us attending to the ultimate limit, our own mortality. Ideally, everyone should contemplate their legacy – what do I want to leave as my accomplishments for future generations? When others remember us

Key elements of a Healthy Brain program
Sense of purpose
Social engagement
Cognitive activity
Physical exercise
Healthy diet
General body function, including sexual health
Self-efficacy
Sustainability
Integrative approach to health

Table 1.

NEUROSCIENCE NURSING PRACTICE CENTER

Erin Supan, CNS
Director

The Neuroscience Nursing Practice Center is dedicated to the development and implementation of best practices in neuroscience nursing. Our mission is to improve patients' long-term outcomes by providing care according to the most advanced protocols based on the latest research findings, offering highly personalized care, and maximizing efficiencies during every stage of treatment. These strategies are implemented throughout the continuum of patient care from first diagnosis, through treatment, to follow-up visits in any location in which the patient is seen. Our program is based on three core principles:

- Evidence-based nursing practice
- Patient-centered care
- Relationship-based nursing

The Neuroscience Nursing Practice Center upholds a strong culture of patient-centered care that extends across every discipline, including rehabilitation, pharmacy, social work, nutrition, and medical services.

by our life stories, our social contribution extends beyond personal death. The deepest model of health should address an individual's spiritual and religious beliefs, if he or she thinks of life's meaning and purpose in those terms.

The Broader Aspects of Brain Health

Having considered the depth of brain health, what do we mean by the broader aspects of cognitive wellness? These aspects of our brain health program link us to community. As a neurologist, I often say that we don't think with just our brains; we, in fact, think with our entire bodies. However, what is not often appreciated is the importance of thinking with other people. Much of cognition is social. Even in physical solitude when reading a book or simply thinking about other people, we engage our thoughts with the thoughts that we imagine other people have. Especially in live conversation, we are thinking collectively (and often emoting together). The concepts of distributed intelligence and the wisdom of crowds capture the idea that we have a better chance of solving problems and creating opportunities together, though sometimes collective folly rather than group wisdom can result, depending on the circumstances.[9]

Let us remember that the health of our communities plays a large role in determining our individual health. Whether we eat healthy foods, exercise, or avoid contact with excessive amounts of pollution or neurotoxins depends in part on the structure of our built and natural environments. Social networking using information technology offers tremendous opportunities for enhancing our collective brain health. In fact, the creation of collective wisdom is critical to our adaptation and survival. No longer should we think of wisdom as the attribute of a few rare and often long-dead people. Brain health recognizes that we are all wise at times (and foolish at others) to varying degrees, but together we can all grow wiser. The opportunities for fostering mutual brain health are great.

The Next Level of Brain Health

So far, we have considered deepening and broadening our concepts of brain health, but are the two related? Depth may appear orthogonal to breadth, but ultimately they may be the same dimension, the same next level of brain health. Whether we have a sense of purpose adequate to drive our brain health activities to a deeper level depends in part on what we wish to contribute to our communities. Many sages have said that we are healthy as a function of putting other people's needs before our own.[10] It is enlightened self-interest to recognize that one's own health depends on the health of other people, and one's sense of purpose depends on connecting to the goals of other people. This broader notion of health that connects us as individuals to other human beings extends to the natural environment. In today's world, we recognize that global climate change is leading to changes in weather patterns and disease epidemiology.[2] For instance, warming contributes to the redistribution of species that can cause infectious disease, and it affects global crop yields and access to water. Thus, we are going to have to be smarter and more committed to each other to survive not just as individuals and communities but as a species that shares ecosystems with other life forms.

How Are We Developing a Model Brain Health Program?

Putting the patient first is an overused and worn expression that often has roots in serving the marketing needs of health care organizations and professions rather than serving people. But the truth of the expression is emerging as we increase our focus on prevention and "behavior change" as ideas that are critical to maintaining and enhancing health. Health is so broad that it requires knowledge from a variety of fields, including medicine, nursing, social work, and psychology. Hence, our program of brain health will involve these core disciplines and others like activity-related therapies and nutrition. We are working with professionals in family medicine, neurology, nursing, and social work to develop our pathways to health. With University Hospitals Neurological Institute as the lead organization, the program hopes to form around partnerships with the Francis Payne Bolton School of Nursing, Fairhill Partners, and other programs at University Hospitals Case Medical Center and Case Western Reserve University School of Medicine as well as community organizations. As such, we plan to continue to integrate research and service learning experiences into our clinical and educational programs for students.

We plan to base one aspect of the practice in The Intergenerational School, a public school that addresses the educational needs of children, adults, and elders. An intergenerational health practice can focus on individual and community health as well as blend medical and educational models of maintaining health.[11] Such a school-based health practice can enhance the role of the school nurse and participate in public health initiatives. Social workers will be involved to address family needs and community resource issues. Psychologists will be available to assist with assessment (clinical psychological and neuropsychological) and treatment.

Yet it is a new model of health coaching that we will incorporate that sends the strongest message about our philosophy of care (Table 2). A coach is a helper, but it is the player (the patient/client) who "competes" in the grand Olympic sport of life. The coach works by sharing expertise as needed, guiding experiences at different levels, and fostering skill development on the way to better performance. The mentoring relationship is key. It is the health life story and the mental images of success that the coach and player co-construct that allows success. As in sports, health emerges from this relationship-based, narrative, holistic practice that is rich with the image of success. With appropriate expert input, health coaching can provide knowledge that ranges from genetic and environmental risk to incorporating so-called complementary and alternative medicine practices. Though always aspiring to evidence-based best practices, an intergenerational practice recognizes the limits of purely data-driven decision making and values the wisdom of collective experience. Planning for the end of life will be appropriately considered earlier than is often the case in health care, as the sages tell us that embracing and planning for our own mortality and legacy can be a part of making life vital and purposeful.

Putting Brain Health Into Collective Action

In Cleveland, we launched our Healthy Brains Healthy Communities Initiative with a keynote speech by Dr. David Satcher, the first African-American surgeon general of the United States and former head of the Centers for Disease Control (Figure 2). This distinguished graduate of Case Western Reserve University has been focusing on the health of children in schools. Our initiative is being conducted in partnership with other health care organizations as well as innovative learning schools. We believe that public schools are an important source of information for young people to begin on a path of brain health and to maintain lifelong learning as a value throughout their lives.

One leading school is The Intergenerational School (TIS), a high-performing, urban community school at Fairhill Center founded by Cathy Whitehouse, myself, and others.[5] TIS is a charter school whose mission is to empower students of all ages to be lifelong learners and spirited citizens. We emphasize experiential learning through community service and create developmentally appropriate educational opportunities for children and elders with cognitive challenges. International, national, and regional recognition has followed as data and stories have demonstrated the value for the school. The school is an organizational innovation that improves public education for kids and creates opportunities for adults, especially elders, to find a meaningful place in the community and to develop a profound sense of legacy. Recently, we conducted quantitative (randomized controlled trial) and qualitative research demonstrating that the school has a positive impact on older volunteers from a local residential facility (Judson Smart Living Community) who have dementia.[6] Hence, our school provides life-enhancing value for learners of all ages in the school, not just the approximately 200 urban children educated there.

We are expanding our brain health activities into the outdoors by working with The Nature Center at Shaker Lakes. Figure 3 shows our award-winning Environmental Protection Agency project (http://www.epa.gov/aging/resources/thesenseofwonder/2009/finalists.html) sharing what Rachel Carson called a sense of wonder about natural systems as we learn about them. Eventually, we hope to have an urban farm associated with our intergenerational brain health practice.

Features of Health Coaching
Places the player (i.e., the patient) first
Is relationship-based
Creates stories and images of positive outcomes
Is practiced by laypersons and the patients themselves
Is purpose driven and goal oriented but reflective
Takes incremental steps and plans long-term outcomes
Pursues continuous quality improvement
Allows access to expertise as needed, e.g., genetic risk
Values aesthetics and artistic expression
Is integrative-holistic

Table 2.

Figure 2: Launching Cleveland's Healthy Brains Healthy Communities Initative on May 18, 2009, with Dr. David Satcher and leaders of local innovative schools and health-oriented community organizations, including (from left to right) Elizabeth Fiordalis (Cleveland Clinic Foundation), Mary Anne Vogel (St. Martin de Porres High School), Brian Driscal (The Urban School), Perry White (Citizens' Academy), David Satcher (Morehouse School of Medicine), Catherine Whitehouse (The Intergenerational School), TJ McCallum (Case Western Reserve University), and David Wright (The Nature Center at Shaker Lakes). The conversation was moderated by Peter Whitehouse (University Hospitals Neurological Institute and Case Western Reserve University). Photo by Peter Whitehouse.

Conclusion

For 10 successful years, we have been prompting this deeper and broader concept of brain health, and we are now joining with like-minded schools, such as the Schools That Can network of high-performing urban schools committed to education of the public. The notion that public schools are a wellspring of energy for improving individual and community health is prompting the University Hospitals Neurological Institute to have one component of its Brain Health Program located in our school. As these programs unfold, we look forward to planned programs at University Hospitals Ahuja Medical Center and to making our contributions to the international conversation about brain health. Brain health, deeply and broadly conceived, is essential to who we are as individual mortal human beings, to what fosters a sense of belonging in our communities, and to how we will face the future ahead. Adding why to this equation is essential. As for where and when, the answer is here and now.

Peter Whitehouse, MD, PhD, is a consultant for SeniorBridge, a geriatric care management company based in New York. This relationship has not affected the content of this article.

Figure 3: Adults and children from The Intergenerational School share a sense of wonder about nature while learning about water systems at The Nature Center at Shaker Lakes. Photo by Peter Whitehouse.

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New Developments in Tay-Sachs Disease

By
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Tay-Sachs disease is one of a family of lysosomal storage disorders known as GM2 gangliosidoses, each determined by the specific peptide (α and ß subunits of ß-hexosaminidase A and the GM2 activator protein) that is defective in the degradation of GM2 ganglioside.[1] The disease is autosomal recessive, caused by a deficiency of the lysosomal enzyme ß-hexosaminidase A that normally degrades GM2 ganglioside. As GM2 ganglioside accumulates in the lysosomes of nerve cells, degeneration of nerve cells results, with gradual loss of nervous system function.

Mutations in the α-subunit of hexosaminidase A are responsible for all forms of the GM2 gangliosidoses – classic infantile Tay-Sachs disease as well as late infantile, juvenile, and late-onset (chronic) forms.[1] Over 75 mutations of the α-subunit gene have been described,[2] resulting in wide variations in residual enzyme activity, the extent and distribution of ganglioside accumulation in the brain and spinal cord, and a great diversity of clinical presentations.[3]

In the classic infantile form, ß-hexosaminidase A is virtually absent, while in the juvenile and late-onset forms residual enzymatic activity persists. The highest carrier rate is among Ashkenazic Jews. However, the incidence has greatly decreased in this population due to widespread carrier screening programs developed in the early 1970s, which has led to a greater than 90% reduction in the annual incidence of infantile Tay-Sachs disease in North America.[3] However, clusters remain among French Canadian and Cajun populations.

Clinical Presentation

Children with infantile Tay-Sachs disease seldom survive beyond the age of five. In contrast, patients with the late-onset form of Tay-Sachs disease generally have onset of symptoms in childhood, usually before the third decade, with survival commonly into adulthood. Lower motor neuron findings predominate, including weakness, muscle wasting, and fasciculations. Cerebellar dysfunction, including tremor, ataxia, and dysarthria are often present, along with upper motor neuron findings (spasticity). Psychiatric dysfunction (recurrent psychosis, depression) is present in at least half the patients and may be the presenting symptom. About a third of patients have a peripheral neuropathy.[4] Extrapyramidal findings are minimal. Occasionally the only presenting symptom may be a childhood stutter.[5] As such, late-onset Tay-Sachs disease is one of a group of atypical motor neuron disorders (Figure 1) that must be distinguished not only from amyotrophic lateral sclerosis but a host of primarily motor disorders with atypical features, including cerebellar, extrapyramidal, cognitive, psychiatric, and/or mild sensory dysfunction.

Atypical Motor Neuron Disorders
Immune-mediated motor neuropathies • multifocal motor neuropathy with conduction block • acute motor axonal neuropathy
Nonimmune-mediated lower motor neuron syndromes • spinal muscular atrophy • progressive muscular atrophy • benign focal amyotrophy
Hereditary spastic paraplegia
Spinocerebellar ataxia with motor neuron involvement
Adult polyglucosan body disease
Post-radiation induced motor neuron dysfunction
Paraneoplastic disorders with motor system involvement
Various toxins and drugs that can affect the motor system

Figure 1. Late-onset Tay-Sachs disease is one of many atypical motor neuron disorders.

Differential Diagnosis

Because lower motor neuron findings predominate in late-onset Tay-Sachs disease, it is not uncommon for patients to initially be misdiagnosed, often with one of the spinal muscular atrophies, such as the Kugelberg-Welander type or progressive muscular atrophy (the lower motor neuron form of amyotrophic lateral sclerosis). If upper motor neuron and cerebellar findings are prominent, patients may be misdiagnosed with multiple sclerosis or hereditary spastic paraplegia. When cerebellar symptoms predominate, patients are often misdiagnosed with spinocerebellar ataxia.

Electrophysiologic testing usually yields normal nerve conduction studies. Needle EMG examination reveals large, prolonged polyphasic motor unit action potentials with abnormal spontaneous activity in the form of fibrillation potentials, positive sharp waves, fasciculations, and, in some patients, complex repetitive discharges.

Clues that should alert the clinician to the diagnosis of late-onset Tay-Sachs disease include the slow progression of a predominant lower motor neuron syndrome with onset before the third decade, a positive family history, spasticity, and signs outside the motor system, including dysarthria, ataxia, tremor, mild cognitive dysfunction, and/or psychosis. There is often a wide variation in phenotype and severity of disease in the same family. The pattern of weakness may be unusual, with a remarkable sparing of some muscle groups, whereas others, such as triceps and quadriceps, are involved early.

Though the disorder is rare, patients with an atypical motor neuron presentation, especially those with cerebellar, extrapyramidal, cognitive, or psychiatric dysfunction that cannot be explained on another basis, should be screened for hexosaminidase A and B deficiency.

Treatment Innovations

There is no cure for Tay-Sachs disease. Supportive therapy consists primarily of symptom management, including physical therapy for gait and balance training, speech therapy for dysarthria, and occupational therapy, if clinically indicated. Importantly, it has been well-known in the Tay-Sachs community that some medications used to treat psychosis and depression can be toxic to lysosomes, and symptoms can be worsened by these medications, including neuroleptics, such as phenothiazines and tricyclic antidepressants, which are best avoided. Lithium carbonate, carbamazepine, and benzodiazepines, alone or in combination, are often the treatment of choice, depending on the psychiatric presentation. These findings were confirmed in a recent study by Shapiro et al.[6]

Several therapeutic interventions have been attempted, and some have recently undergone clinical trials. In the past, therapeutic enzyme replacement[7] and bone marrow transplantation performed on individual patients has shown no benefit in Tay-Sachs infants. While intravenous administration of enzyme replacement therapy has been effective in the treatment of some of the non-neuronopathic lysosomal storage disorders, the blood-brain barrier presents a tremendous obstacle to this type of therapy in Tay-Sachs disease, where central nervous system dysfunction predominates, as delivery of the enzyme across the blood-brain barrier is inadequate.

Another therapeutic avenue that has been tried is substrate deprivation therapy. The rationale behind this therapy is that if synthesis of the glycolipid substrate is inhibited or reduced, then the deficient enzyme is no longer needed in as great a quantity to degrade the substrate. This approach has proven effective in some of the lysosomal storage disorders, such as non-neuronopathic Gaucher disease.[8,9] A trial of miglustat in the treatment of late-onset Tay Sachs disease was conducted at University Hospitals under my direction.[10] Miglustat is a reversible inhibitor of glucosylceramide synthase, the enzyme that catalyzes the first committed step in the synthesis of lacto- and globo-series glycolipids, and has known distribution in the central nervous system. Unfortunately, no definite therapeutic benefit was seen using a variety of test measures in a group of patients with late-onset Tay-Sachs disease. While the negative results were disappointing, the trial had several limitations that may have contributed to the finding of no therapeutic efficacy, including the lack of disease-specific markers, the small patient sample size, the wide clinical variation among patients, and the slow progression of the disease that may have made therapeutic benefit difficult to capture.

A clinical trial is currently underway using a chemical chaperone in patients with late-onset Tay-Sachs disease. Chemical chaperones are small molecules that act as reversible competitive inhibitors to bind the residual enzyme (protein) and facilitate the proper folding of the mutant protein to its native shape, thereby allowing it to be transported to its proper location.[11] In the case of Tay-Sachs disease, the chaperone allows the protein to be transported from the endoplasmic reticulum into the lysosome.[12] Chaperone molecules are only effective when there is enough residual enzyme to bind the chaperone molecule. Furthermore, chaperones are mutation specific and can only refold mutant proteins with a specific conformation that can bind the chaperone to allow it to be refolded. This treatment has been effective in a few case reports of individual patients with lysosomal storage disorders[13] and may prove to be very effective in the chronic forms of Tay-Sachs disease, where residual enzyme persists.

Conclusion

Targeted gene therapy and neural stem cell transplantation are other modes of treatment that may prove effective. Currently, the Tay-Sachs Gene Therapy Consortium is conducting experiments with small and large animals to find the right viral vector to transfer the gene, with the intention of beginning a gene therapy clinical trial in patients with Tay-Sachs disease in the next couple of years. Other possible treatment options include oligonucleotide recombination, which exchanges synthetic oligonucleotides with a normal DNA sequence for the mutant DNA sequence in vivo and may have promise in the future.[14] In the final analysis, a combination of treatments may hold the most promise.

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