The 2014 Rush Neuroscience Review
As we see patients in our clinics, we are reminded on a daily basis of the reasons why growth is so exciting and so critical.

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Chairperson, Department of Neurological Surgery

Jacob Fox, MD  
Chairperson, Department of Neurological Sciences
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Chairmen’s Letter

“Growth” is not a word that typically conjures positive images in the clinical neurosciences. As neurologists and neurosurgeons, we often view “growth” in reference to life-threatening pathologies endangering our patients. Clinically, growth is often something to fight.

As chairs, however, we welcome growth and the challenges it presents: How can we get patients with these life-threatening diseases into clinic as quickly as possible? How can we ensure that greater numbers of stroke patients in our region receive neurologic stroke expertise in a timely manner through additional telemedicine partners?

These are only two examples of the positive growth challenges we have been fortunate to face in the last year. As evidenced in our quality data (see page 68), our neurological inpatient discharges have grown each year for the past five years, with an increase of more than 30% since 2009. We are pleased to share with you some of our additional highlights from the past year in The 2014 Rush Neuroscience Review:

**Expanded skull base and pituitary surgical capabilities:** Upon arrival in January 2014, new Department of Otorhinolaryngology chairperson Pete Batra, MD, immediately began collaborating with his neurosurgical and neuro-oncology colleagues to expand the existing services for these patients. The new Rush Center for Skull Base and Pituitary Surgery brings together colleagues in 11 specialties to provide truly comprehensive, multidisciplinary care.
Additional neurointensivists: As one of the busiest neurointensive care units in Illinois, we are always looking for ways to improve care delivery for this vulnerable patient population. We now have seven board-certified neurointensivists working closely with our colleagues in neurosurgery, anesthesia and radiology to treat the more than 150 patients we see on average each month.

Growth of spine services: In 2013, Richard Fessler, MD, PhD, joined our spine team, bringing additional capabilities in minimally invasive spine repair for scoliosis and revision back surgery. Our team performed more than 800 spine and nerve surgeries last year. With the addition of another new surgeon this summer, we are poised to provide relief to even more patients with spine tumors, injuries and deformity over the next year.

Patient access: We continue to focus on getting patients with emergent neurologic issues into our clinics as quickly as possible. To that end, we offer appointments within two weeks—or, if needed, the next day—to patients requesting an appointment with a neurologist. Since we began this expedited access in August 2011, our neurology practice has averaged more than 400 new patients per month.

Advanced care for medically refractory epilepsy: In fall 2013, patients with medically refractory epilepsy welcomed the news of FDA approval of the RNS system (Neuropace)—a device epileptologists at Rush helped investigate throughout its clinical trials. While many centers now offer this option to patients, Rush is the first center in Illinois to combine the RNS system with a unique brain mapping system created by epileptologist Marvin Rossi, MD, PhD. The system facilitates the surgical placement of electrodes at the precise location in the brain’s temporal lobe circuitry. In trials, Rossi found that Neuropace combined with his mapping system reduced seizures by up to 50 percent in patients with medically refractory epilepsy.

Translational research: Even as we are experiencing exciting clinical growth and medical advances, clinicians in our respective departments continue to conduct and publish translational research aimed at uncovering disease processes and improving our patients’ lives. See pages 56–64 for a sampling of last year’s published research endeavors.

As we see patients in our clinics, we are reminded on a daily basis of the reasons why growth is so exciting and so critical: With our aging population intersecting with advances in medicine, there are ever more patients to treat, a greater array of potential treatment interventions and expanding pathways of research exploration.

This intersection of need and possibility, combined with truly outstanding colleagues poised to tackle it, is what makes our work as neuroscientists at Rush both humbling and stimulating. And in this journal, we invite you to enjoy a sampling of the exemplary work of our faculty.

Regards,

Richard Byrne, MD
Chairperson, Department of Neurological Surgery
The Roger C. Bone, MD, Presidential Chair

Jacob Fox, MD
Chairperson, Department of Neurological Sciences
The Joseph and Florence Manaster Foundation Professor of Multiple Sclerosis
Primary and Associated Faculty (2013)

Department of Neurological Sciences

Chairperson: Jacob Fox, MD

Alzheimer’s disease

Neelum Aggarwal, MD
Konstantinos Arfanakis, PhD
Lisa Barnes, PhD
David Bennett, MD
Patricia Boyle, PhD
Aron Buchman, MD

Ana Capuano, PhD
Robert Dawe, PhD
Debra Fleischman, PhD
S. Duke Han, PhD
Bryan James, PhD
Sue Leurgans, PhD

Sukriti Nag, MD, PhD
Julie Schneider, MD
Raj Shah, MD
Rita Shapiro, DO
Robert Wilson, PhD
Lei Yu, PhD

Not pictured:
Zoe Arvanitakis, MD
Denis Evans, MD

Cerebrovascular disease

James Conners, MD, MS
Shawna Cutting, MD
Michael Kelly, MD
Vivien Lee, MD
Laurel Smit, MD
Sarah Song, MD

Clinical neurophysiology and epilepsy

Antoaneta Balabanov, MD
Donna Bergen, MD
Lawrence Bernstein, MD
Adriana Bermeo-Ovalle, MD
Thomas Hoeppner, PhD
Serge Pierre-Louis, MD

Marvin Rossi, MD, PhD
Michael Smith, MD

Not pictured:
Esmeralda Park, MD
Michael Stein, MD
Travis Stoub, PhD
Cognitive neurosciences

Not pictured:
Mehul Trivedi, PhD

Critical care neurology

Richard Temes, MD

Not pictured:
Robert Wright, MD

Movement disorders

Not pictured:
Melany Danehy, MD
Bichun Ouyang, PhD
Glenn Stebbins, PhD
Multiple sclerosis

Roumen Balabanov, MD
Rajendra Goswami, PhD
Dusan Stefosi, MD
James Stewart, PhD

Not pictured: Michael Ko, MD

Neurobiology

Yaping Chu, PhD
Leyla deToledo-Morrell, PhD
Dean Hartley, PhD
Bin He, PhD
Jeffrey Kordower, PhD
Kalipada Pahan, PhD

Sylvia Perez, PhD

Not pictured: Malabendu Jana, PhD
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Dan Nicholson, PhD
Avik Roy, PhD
Dustin Wakeman, PhD
Shunbin Xu, MD, PhD

Neuromuscular disease

Irwin Siegel, MD
Madhu Soni, MD

Not pictured: Alex Barboi, MD
John-Michael Li, MD

Neuro-oncology

Robert Aiken, MD
Nina Paleologos, MD

Neuro-ophthalmology

Thomas Mizen, MD
Aimee Szewka, MD

Pediatric neurology

Elizabeth Berry-Kravis, MD, PhD
Peter Heydemann, MD

Not pictured: Lubov Romantseva, MD
Primary and Associated Faculty (2013)

Department of Neurological Surgery

**Chairperson:** Richard Byrne, MD

![Richard Byrne, MD](image1)
![Michael Chen, MD](image2)
![Harel Deutsch, MD](image3)
![Richard Fessler, MD, PhD](image4)
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![Roham Moftakhar, MD](image6)

![Lorenzo Muñoz, MD](image7)
![John O’Toole, MD](image8)
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Research faculty

Roberta Glick, MD
Terry Lichtor, MD, PhD
Richard Penn, MD

Associated faculty at Rush University Medical Center

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Sheila Dugan, MD  
Physical medicine and rehabilitation
R. Mark Wiet, MD  
Neurology

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Mary Sturaitis, MD, anesthesiology

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George Bovis, MD  
Martin Herman, MD, PhD
Juan Jimenez, MD  
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Sepehr Sani, MD  
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Fellows and Residents (2013)

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Residency: Rush University Medical Center

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Michael Boyd, MD  
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Residency: Northwestern University Feinberg School of Medicine

Arli Bumatayo, MD  
Medical school: University of Santo Tomas Medical School, Philippines  
Residency: Overlook Medical Center

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Medical school: Drexel University College of Medicine  
Residency: Rush University Medical Center

Melissa Mercado, MD  
Medical school: Boston University School of Medicine  
Residency: Boston University Medical Center

Gian Pal, MD  
Medical school: Robert Wood Johnson Medical School  
Residency: Georgetown University Medical Center

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Residency: Rush University Medical Center

Rochelle Sweis, DO  
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Residency: Froedtert Memorial Lutheran Hospital

Erick Tarula, MD  
Medical school: David Geffen School of Medicine at UCLA  
Residency: Beth Israel Deaconess Medical Center

Padmaja Vittal, MD  
Medical school: M.S. Ramaiyah Medical College, India  
Residency: Tulane University School of Medicine

**Residents**

Anik Amin, MD  
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Medical school: University of Louisville School of Medicine

Ankush Bhatia, MD  
Medical school: Rush Medical College

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Medical school: New York University School of Medicine

Arun Chhabra, MD  
Medical school: Eastern Virginia Medical School

Danielle Detterman, MD  
Medical school: Northeastern Ohio Universities College of Medicine

Kathryn Ess, MD  
Medical school: Indiana University School of Medicine

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Medical school: Rush Medical College

Avram Fraint, MD  
Medical school: Rush Medical College

Michael Gibbs, MD  
Medical school: Northwestern University Feinberg School of Medicine

Sabreena Gillow, MD  
Medical school: University of Colorado Denver School of Medicine

Breyanna Grays, MD  
Medical school: Indiana University School of Medicine

Carrie Grouse, MD  
Medical school: University of Virginia School of Medicine

Christian Hernandez, MD  
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Matthew Raday, MD  
Medical school: Rush Medical College

Sarah Sung, MD  
Medical school: University of Oklahoma College of Medicine

Jessica Templer, MD  
Medical school: Chicago Medical School

Jaspreet Thiara, MD  
Medical school: Rush Medical College
Department of Neurological Surgery

Fellows

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Residency: University of Texas Medical Branch at Galveston

Nakhle Mhanna, MD
Medical school: Lebanese University Faculty of Medical Sciences
Residency: Lebanese University, Faculty of Medical Sciences
  orthopedic surgery

David Stidd, MD
Medical school: University of Texas Southwestern Medical School
Residency: University of Arizona College of Medicine

Residents

Sumeet Kumar Ahuja, MD
Medical school: Indiana University School of Medicine

Ricardo Fontes, MD, PhD
Medical school: University of São Paulo School of Medicine

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Stephan Munich, MD
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Joshua Wewel, MD
Medical school: University of Nebraska Medical Center College of Medicine
Faster Cognitive Decline in the Years Prior to Magnetic Resonance Imaging Is Associated With Smaller Hippocampal Volumes in Cognitively Healthy Older Persons

Debra A. Fleischman, PhD; Lei Yu, PhD; Konstantinos Arfanakis, PhD; S. Duke Han, PhD; Lisa L. Barnes, PhD; Zoe Arvanitakis, MD, MS; Patricia A. Boyle, PhD; David A. Bennett, MD

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Introduction

Early identification of persons at risk for cognitive decline in aging is critical to optimizing treatment to delay or avoid a clinical diagnosis of dementia due to Alzheimer’s disease (AD).1,2 Accordingly, the diagnostic continuum of AD has recently been reconceptualized to emphasize clinical AD diagnosis as the final stage of the disease, and attention has shifted to characterizing cognitive and biologic markers in a preclinical phase that can reliably identify those persons at increased risk of ultimately developing clinical AD.3,4

This preclinical phase, during which subtle cognitive changes are occurring in some cognitively healthy older persons, can be quite long, potentially lasting many years.5-8 Cognitively healthy persons who are experiencing subtle cognitive decline within the normal range may be undergoing a clinically silent pathological cascade of brain changes during this phase.9,12 One of those brain changes, hippocampal atrophy, is thought to occur late in this cascade and, when it is associated with overt cognitive impairment, may mark the transition out of the preclinical phase. Indeed, the association between hippocampal atrophy and mild cognitive impairment (MCI) and AD is a well-established finding in cross-sectional and prospective longitudinal studies.4,11,13-16

The association between hippocampal atrophy and cognitive function in cognitively healthy persons in both cross-sectional and prospective longitudinal studies, however, is not as clear. Medial-temporal, including hippocampal, volume loss has been reported and associated with cognitive function in a number of studies of older persons considered cognitively normal,17-28 but just as many other studies find that this association is weak or not present.19,29-37

At least three important reasons explain the mixed findings. First, studies do not always distinguish between participants who are and are not declining in cognitive function within the normal range.38 Further, using a single measure of global cognitive function limits what can be learned about specific aspects of cognitive function and cognitive decline that may be associated with brain integrity. Thus, there is a need for a longitudinal study that examines the association between hippocampal atrophy, a well-established biomarker for MCI and AD, and change in cognition during the phase when older persons are considered cognitively healthy, across many cycles during this protracted phase, using measures of global cognition and specific domains of cognition that are known to be sensitive to change within the normal range.7,8

In this study, we examined cognitive change and its association with hippocampal atrophy during the cognitively healthy years leading up to structural imaging. The Rush Memory and Aging...
Project, a longitudinal cohort study of aging and dementia, began in 1997 and introduced neuroimaging in 2009. Therefore, we were able to measure the rate of global cognitive change, as well as the rate of change in 5 specific cognitive systems, in multiple years leading up to structural brain imaging in clinically well-characterized persons who did not have MCI or dementia at the time of scan. We tested the hypothesis that older persons who experienced faster decline in cognition, but who were still considered cognitively healthy at the time of scan, would have smaller hippocampal volumes.

Materials and Methods

Participants

The participants are part of an ongoing longitudinal cohort study of aging and dementia. The Rush Memory and Aging Project has a rolling admission and requires annual clinical evaluation and brain donation at death.39 The study was approved by the institutional review board of Rush University Medical Center.

At the time of analyses, 1528 participants had enrolled and completed their baseline evaluation: 564 died, 107 refused further participation in either the parent study or the neuroimaging substudy before scan data could be collected, and 342 were not eligible for the scan because of various reasons including magnetic resonance imaging (MRI) contraindications. Of the remaining 315 participants, 440 were scanned and 75 were being scheduled for scanning. Of the 440 participants who were scanned, 414 had data on hippocampal volume, of whom 8 had dementia at scan and 138 had only one cognitive data point prior to scan. Of the remaining 268 participants, 57 had mild cognitive impairment and 211 were cognitively normal.

Clinical Evaluation

All participants underwent an annual uniform and structured clinical evaluation that included a medical history, a complete neurological examination, and cognitive performance testing. On the basis of these data and in-person evaluation of the participants, an experienced clinician diagnosed dementia and AD using the criteria of the joint working group of the National Institute of Neurologic and Communicative Disorders and Stroke and the Alzheimer Disease and Related Disorders Association.40 The criteria require a history of cognitive decline and impairment in at least 2 cognitive domains, one of which must be memory for a diagnosis of AD. As previously described,39 impairment in 5 cognitive domains (orientation, attention, memory, language, and visuospatial ability) was determined in a 2-step process. First, an algorithm rated impairment in each domain on the basis of educationally adjusted cutoff scores on 11 individual tests. Second, on the basis of all test data and information on education, sensorimotor problems, and effort, a neuropsychologist agreed or disagreed with each rating and supplied a new rating in the event of disagreement. Persons who had cognitive impairment but did not meet criteria of dementia were classified as having MCI. All clinical classification was done blinded to previously collected data.

Cognitive Evaluation

A battery of 21 cognitive performance tests was administered in an approximately hour-long session during baseline and annual follow-up sessions. The Mini-Mental State Examination (MMSE) was used as an overall measure of cognitive ability, and one test (Complex Ideational Material) was only used for diagnostic classification.39 Episodic memory measures included Word List Memory, Word List Recall, and Word List Recognition from the procedures established by the Consortium to Establish a Registry for Alzheimer’s Disease, immediate and delayed recall of Logical Memory Story A and the East Boston Story. Semantic memory measures included Verbal Fluency, Boston Naming, and a subset of items from the National Adult Reading Test. Working memory measures included the Digit Span subtests (forward and backward) of the Wechsler Memory Scale–Revised and Digit Ordering. Measures of perceptual speed included the oral version of the Symbol Digit Modalities Test, Stroop Test, and Number Comparison. Measures of visuospatial ability included Judgment of Line Orientation and Standard Progressive Matrices. Raw scores on each test were converted to standard $z$ scores using the mean and standard deviation from the baseline evaluation. A person’s standard scores across 19 tests were averaged to yield a single overall cognitive composite score. A composite score for 5 cognitive domains (episodic memory, semantic memory, working memory, perceptual speed, visuospatial ability) was created by averaging the $z$ scores of all measures within a domain.39

MRI Acquisition and Postprocessing

MRI scans were performed on a 1.5-Tesla General Electric MRI scanner (GE, Waukesha, Wisconsin). High-resolution T1-weighted anatomical data were obtained for all participants using a 3-dimensional magnetization-prepared rapid acquisition gradient-echo sequence with the following parameters: TE = 2.8 msec, TR = 6.3 msec, preparation time = 1000 msec, flip angle 8°, field of view 24×24 cm, 160 sagittal slices, 1-mm slice thickness, no gap, 224×192 image matrix reconstructed to 256×256, scan time = 10 minutes 56 seconds. Two copies of the T1-weighted data were acquired on each participant. The two T1-weighted data sets from each participant were coregistered using rigid-body registration and averaged. The average T1-weighted data set of each participant was then segmented using FreeSurfer Version 5 (http://surfer.nmr.mgh.harvard.edu).41,42 The results were reviewed and any errors were manually corrected. The volume of the segmented gray matter regions, including the hippocampus, and the total intracranial volume were estimated for each participant. The volumes of homologous regions in contralateral hemispheres were averaged. Finally, hippocampal and all other volumes were normalized by dividing by the total intracranial volume (ICV).

Daily quality assurance tests were conducted on the scanner according to the American College of Radiology protocol. The data from these tests were used to evaluate the performance of the MRI scanner hardware on days when data on participants were collected. An algorithm developed in house was used to automatically produce the results of the quality assurance tests.
Furthermore, the whole-brain signal to noise ratio (SNR) and the contrast to noise ratio (CNR) between white and gray matter were estimated for the average T1-weighted data set of each participant. The mean and standard deviation of the SNR and CNR were calculated over all participants. Individual data sets with SNR or CNR lower than 2 standard deviations from the mean SNR and CNR over all participants were inspected for potential problems in the raw data or with automated brain segmentation. Finally, the data were inspected for outliers in ICV-normalized volumes.

**Statistical Approach**

To investigate the temporal association between the prescan rate of change in cognition with total hippocampal volume, we first estimated the slope of cognitive decline for each individual by fitting a linear mixed model to all available longitudinal cognitive testing data up until the time of neuroimaging, adjusted for age, sex, and years of education. These person-specific slopes were then used in ordinary linear regression as the predictor for hippocampal volume. All subsequent regression models were also adjusted for age at scan, sex, and education.

We first examined the association of prescan rate of change in global cognition with hippocampal volume. Next, because it is possible that the association may differ across cognitive domains, in subsequent analyses we examined the association of the rates of change in 5 different cognitive domains of episodic memory, semantic memory, working memory, perceptual speed, and visuospatial ability with hippocampal volume. Finally, because the presence of vascular disease burden or vascular disease risk might influence the association of prescan change in cognition with the hippocampal volume, in secondary analyses we augmented our core model by adding covariates for vascular disease burden (a composite score of vascular diseases including claudication, stroke, heart conditions, and congestive heart failure) as well as vascular disease risk (a composite score of vascular disease risk factors including hypertension, smoking, and diabetes). We imposed a nominal threshold of \( P < .05 \) for statistical significance, and all analyses were implemented using SAS software, version 9.3.41

### Results

The analysis included 211 participants who were part of the Rush Memory and Aging Project. Descriptive characteristics of the group are provided in Table 1. The mean age at scan was 82.7 years (SD = 6.7 years; range, 65.2-100.3 years). The average length of follow-up prior to imaging was 5.5 years (SD = 2.7 years; range, 0.6-13.0 years). Comparing this sample with the participants who were scanned but were excluded from the analysis because of dementia or lack of follow-up data, we found no significant differences between the two samples in age, sex, or education. Participants who were excluded from the analysis had, on average, lower global cognitive function (\( P < .001 \)) and fewer vascular diseases (\( P < .001 \)). The difference in vascular disease risk was marginal (\( P = .086 \)).

Quality assurance testing demonstrated that scanner performance was satisfactory and consistent. The SNR and CNR of all data sets included in this study exceeded the minimum acceptable limits. No outliers in ICV-normalized hippocampal volumes were identified.

Average ICV-normalized hippocampal volume was \( 4.1 \times 10^{-3} \) (SD = \( 0.7 \times 10^{-3} \); range, \( 2.7 \times 10^{-3} \) to \( 6.5 \times 10^{-3} \)). Simple correlation analyses revealed that hippocampal volume was negatively associated with age at scan (\( r = -0.57, P < .001 \)) and positively associated with global cognition at scan (\( r = 0.26, P < .001 \)) and MMSE score (\( r = 0.26, P < .001 \)). Hippocampal volume was not related to years of education. In this group, females had larger hippocampal volumes than males (\( D = 0.36 \times 10^{-3}, t = 3.87, df = 128.3, P < .001 \)).

To examine the association of prescan rate of change in cognitive function with hippocampal volume, we first constructed a linear mixed-effects model with a term for time (since baseline in years) to estimate each person's annual rate of global cognitive change (ie, slope), adjusted for age, sex, and education. On average, there was no overall decline in global cognition (Estimate = \(-0.004, SE = 0.004, P = .273 \)). However, because some persons declined, others remained the same, and still others improved as a result of practice and learning, the variance estimate for person-

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at scan, mean (SD), y</td>
<td>82.7 (6.7)</td>
</tr>
<tr>
<td>Education, mean (SD), y</td>
<td>15.3 (3.1)</td>
</tr>
<tr>
<td>Female, no. (%)</td>
<td>154 (73.0%)</td>
</tr>
<tr>
<td>MMSE score at scan, mean (SD)</td>
<td>28.7 (1.3)</td>
</tr>
<tr>
<td>Global cognitive score at scan, mean (SD)</td>
<td>0.38 (0.44)</td>
</tr>
<tr>
<td>Total hippocampal volume,* mean (SD)</td>
<td>( 4.1 \times 10^{-3} ) (( 0.7 \times 10^{-3} ))</td>
</tr>
<tr>
<td>Prescan follow-up, mean (SD), y</td>
<td>5.5 (2.7)</td>
</tr>
<tr>
<td>At least one vascular disease, no. (%)</td>
<td>82 (38.9%)</td>
</tr>
<tr>
<td>At least one vascular risk factor, no. (%)</td>
<td>170 (80.6%)</td>
</tr>
</tbody>
</table>

Abbreviation: MMSE, Mini-Mental State Examination.

*Normalized by dividing by the total intracranial volume.

**Table 1.** Descriptive Characteristics of the Participants in the Study (N = 211)
specific slopes was highly significant (Estimate = 0.0007, SE = 0.0002, \( P < .001 \)). Figure 1 illustrates the predicted linear decline in global cognition for a randomly selected sample of 20 persons. Figure 2 further illustrates the distribution of person-specific prescan rates of decline (mean = −0.005; SD = 0.019; range, −0.057 to 0.039). As shown in these figures, even among these cognitively healthy persons, the rates of decline show a sizeable amount of variability: some persons declined faster, some declined more slowly, and other persons improved slightly.

To illustrate the difference in hippocampal volumes between cognitively healthy persons with declining slopes (cognitive decliners, 57.8% of the sample) and cognitively healthy persons with nonnegative slopes (cognitive maintainers, 42.2% of the sample), we present a prism-like plot showing the mean difference in hippocampal volume between the groups. Figure 3 shows that persons who declined in cognitive function prior to the time of scan had on average smaller hippocampal volumes.

Next, to formally test the hypothesis that faster rate of decline in global cognitive function prior to scan was associated with smaller hippocampal volume, we constructed a linear regression model with hippocampal volume as the outcome and terms for global cognitive slope, age at scan, sex, and education as the predictors. The result of this analysis showed that a more rapid rate of prescan cognitive decline was associated with smaller hippocampal volume (\( P = .019 \); Table 2). To clarify the magnitude of this effect, when the rate of prescan decline in global cognition increased by 1 standard deviation, the average reduction in total hippocampal volume was equivalent to an increase of about 2 years of age. The results were unchanged after adjusting for vascular disease burden and vascular disease risk.

Finally, we examined the association of rates of change in domain-specific summary measures of cognition with hippocampal volume. Analyses of 5 different cognitive domains indicated that smaller hippocampal volume was associated with faster prescan decline in working memory (\( P = .017 \)). There was also a strong trend for smaller hippocampal volume to be associated with prescan decline in episodic memory (\( P = .059 \)). Hippocampal volume was not associated with prescan decline in semantic memory, perceptual speed, or visuospatial ability.

**Discussion**

The results of this study demonstrate that when cognition is fully characterized over a sufficient period during the phase when older persons are considered cognitively healthy, substantial...
individual variability in slopes of cognitive change is observed and a faster rate of cognitive decline, particularly in working memory, can be linked to hippocampal atrophy, a well-established biomarker of risk for MCI and/or AD.

Our findings are consistent with a number of studies that report cognitive decline in the healthy years preceding a clinical diagnosis of MCI and/or AD and extend these results by underscoring the substantial variability in cognitive function that occurs within the normal range during these years. Some persons decline, some stay stable, and others improve, and this heterogeneity may be one explanation for mixed findings regarding the relationship of cognitive decline to measures of brain integrity in the cognitively healthy years. In this study, those persons who were cognitively healthy at the time of scan, but who declined cognitively in the years preceding the scan, had smaller hippocampal volumes.

We measured cognitive decline globally, but also in 5 different domains, and found that the association with smaller hippocampal volume was driven most strongly by decline in working memory. This finding is in line with studies that have connected the soundness of working memory in aging to the integrity of the hippocampal region. However, the association between episodic memory and hippocampal atrophy was weaker, a finding that is often noted in studies of cognitively healthy older persons. When we separated our sample into domain-related decliners and maintainers, the percentage of working-memory decliners was quite high (97%) and the association with hippocampal atrophy was strong, whereas the percentage of episodic-memory decliners was quite low (14%) and the association with hippocampal atrophy was marginal. Again, these findings emphasize the importance of addressing sample composition in longitudinal studies of cognition and brain integrity in cognitively healthy older persons. Most importantly, however, they suggest that older persons who are considered cognitively healthy but have evidence of cognitive decline, particularly in working memory, may be amid a pathological cascade and on a protracted trajectory toward neuronal injury, episodic memory impairment, and eventually a clinical diagnosis of MCI or AD.

Many studies have established that maintaining cognitive function in older age lowers the risk of adverse cognitive and functional outcomes; however, the association of cognitive maintenance with brain integrity is not well studied. Only one study that we know of has examined the relationship of cognitive maintenance to brain integrity in cognitively healthy older persons in the years prior to imaging. Rosano et al reported that 59% of persons in their sample maintained global cognitive function, based on the Modified Mini-Mental State Examination (3MS), over 4 time points in the decade prior to the time of scan. Cognitive maintainers had larger medial temporal lobe (hippocampus, parahippocampus, entorhinal cortex) gray matter volumes. The results of the current study support this finding in that global cognitive maintainers (42.2% of our sample) had larger hippocampal volumes compared to cognitive decliners. However, the possibility that cognitive maintenance reflects susceptibility to practice effects needs to be addressed. We examined this possibility in secondary analyses using scores from the cognitive domain that generated the largest percentage of cognitive maintainers, episodic memory (86%). We added additional terms to the linear mixed models representing the number of follow-up years of cognitive testing, as previously reported. We found some evidence of a practice effect on episodic memory; however, the percentage of episodic memory maintainers still reached 60% after adjusting for this practice effect. This finding suggests that these individuals are genuinely maintaining or improving their episodic memory. A number of lifestyle behaviors that can potentially protect cognition have been examined. For example, it has been shown that frequent mental stimulation leads to better cognitive function, particularly in episodic memory. More studies are needed to further understand the brain basis of this phenomenon.

This study has important strengths. The data were sampled from a large, longitudinal clinical-pathological study in which participants have had up to 14 annual assessments using well-established clinical and cognitive measures. The study also has limitations. The period over which cognitive change was measured in this study cannot be considered preclinical. All participants were cognitively healthy at time of scanning, and we await clinical outcomes. Although the Rush Memory and Aging Project was designed to closely represent the general population of persons aged 65 years and older, the sample in this

<table>
<thead>
<tr>
<th>Cognitive Measure</th>
<th>Estimate* (SE)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global cognition</td>
<td>0.055 (0.023)</td>
<td>.019</td>
</tr>
<tr>
<td>Episodic memory</td>
<td>0.033 (0.017)</td>
<td>.059</td>
</tr>
<tr>
<td>Semantic memory</td>
<td>0.042 (0.045)</td>
<td>.347</td>
</tr>
<tr>
<td>Working memory</td>
<td>0.065 (0.027)</td>
<td>.017</td>
</tr>
<tr>
<td>Perceptual speed</td>
<td>0.017 (0.010)</td>
<td>.112</td>
</tr>
<tr>
<td>Visuospatial ability</td>
<td>−0.106 (0.129)</td>
<td>.414</td>
</tr>
</tbody>
</table>

*Estimates refer to the increase in hippocampal volume (× 10⁻³) with every 0.01 unit increase in rate of change in cognition. All the models were adjusted for age at scan, sex, and years of education.

Table 2. Prescan Rate of Change in Cognition and Hippocampal Volume

The 2014 Rush Neuroscience Review
study was selected. Multiple years of cognitive data allowed the examination of cognitive change, but the volume data are from one time point. Thus these data cannot address simultaneous change in prescan cognition and hippocampal volume.

However, participants of the Rush Memory and Aging Study agree to biannual scanning until death, so it will be possible to examine the associations between cognitive change, transition to clinical diagnoses, and macrostructural change in the future. Hippocampal volume in elderly individuals may be influenced by the presence of not only AD pathology but other pathologies such as hippocampal sclerosis, Lewy bodies, and amyloid angiopathy. Although we cannot address the neuropathology of reduced volume in this study, histopathologic information will be available for these participants in the future. Finally, a stronger magnet would have allowed a closer examination of associations with hippocampal volumes in specific subfields. In studies in which a 4-Tesla magnet was used, the CA1 subfield has been shown to be most strongly affected by age, particularly in the seventh decade and hippocampal deformation was primarily attributable to CA1 volume loss in a postmortem imaging shape analysis of persons older than 65 years. Postmortem imaging will also be available for these participants in the future. These limitations notwithstanding, the results of this study are important for at least 2 reasons. First, they emphasize the need to deeply characterize cognition, brain structure, and their relation during the years in which older persons are considered cognitively healthy. Second, the findings are clinically relevant. Whereas clinicians often use imaging biomarkers such as hippocampal volume to predict subsequent cognitive decline, these findings show that hippocampal volume can inform the clinician on the trajectory of cognitive change during the period preceding the patient’s first presentation to the clinic. This information would help the clinician elucidate the patient’s cognitive history, identify the patient’s risk of developing a clinical diagnosis of MCI or dementia due to AD, and optimize treatment.

References are available online at www.rush.edu/neurosciencereview.
Mechanism-Based Treatments in Neurodevelopmental Disorders: Fragile X Syndrome

Elizabeth Berry-Kravis, MD, PhD

In the past decade, the study of the neurobiology and synaptic mechanisms in fragile X syndrome (FXS) has emerged as a molecular doorway to future targeted treatments for autism and related developmental disorders. FXS is the most common identifiable genetic cause of intellectual disability and autism, with an estimated frequency of about 1 in 4,000 to 5,000. The disorder affects all ethnic groups worldwide.

FXS is one of a group of fragile X-associated disorders arising from trinucleotide repeat (CGG) expansion mutations in the promoter region of FMR1 (fragile X mental retardation 1 gene; Figure 1). The CGG sequence is transcribed into the FMR1 mRNA but is located in the 5’ untranslated region of the mRNA, and thus length of this sequence does not affect the sequence of the protein product of the FMR1 gene (fragile X mental retardation protein, or FMRP). Smaller mutations in the gene (55-200 CGG repeats) termed the “premutation” occur in about 1 in 151 to 209 females and 1 in 430 to 468 males in the United States and are associated with risk for fragile X-associated tremor/ataxia syndrome and fragile X-associated primary ovarian insufficiency, through a mechanism thought to relate to elevated FMR1 mRNA levels and resultant CGG repeat-mediated RNA toxicity.

Large expansions in FMR1 (> 200 repeats), termed the “full mutation,” cause FXS, which results from the methylation and transcriptional silencing of the FMR1 promoter with consequent loss or significant reduction of expression of FMRP. Expansions in FMR1 tend to increase in size as they are inherited from generation to generation, and thus fragile X-associated disorders affect families in multiple generations.

Male patients with FXS typically display intellectual disability that can range from mild to severe, with characteristic patterns of strength and weakness in specific cognitive, language, and executive domains. Affected individuals most commonly present with language delay. Hypotonia is often seen early in life and evolves into coordination and praxis problems by school age. Physical features include macro-orchidism in most adult males, and variable presence of prominent ears, macrocephaly, long face, prominent jaw and forehead, midfacial hypoplasia, high arched palate, and loose connective tissue leading to hyperextensible joints, flat feet, and soft skin. Characteristic behavioral features include hyperactivity, impulsivity, attention problems, anxiety, mood lability, and autistic features such as poor eye contact, shyness, self talk, hand flapping, hand biting, hyperarousal to sensory stimuli, and substantial perseverative language and behavior. Approximately one-third of male patients with FXS meet criteria for autism, and two-thirds, for an autism spectrum disorder (ASD). Medical problems commonly include seizures (about 15%, usually in childhood) and strabismus (10%-30%), whereas frequent ear infections, gastroesophageal reflux, sleep apnea and other sleep disorders, loose stools, and allergies are thought to be more prevalent in patients with FXS than in the general population. Female patients with a full mutation are more variably and typically more mildly affected than males because of the production of FMRP from the normal FMR1 allele.
in cells expressing the nonmutated X chromosome. Severity of cognitive impairment in female patients with the full mutation is inversely related to the activation ratio for the normal FMR1 allele and the expression of FMRP. Males with mosaicism for a full mutation and premutation or a partially unmethylated full mutation may be more mildly affected, with severity related to the amount of unmethylated DNA and FMRP levels.

Current treatment of FXS is supportive and includes therapy, educational strategies that take into account cognitive and behavioral strengths and weaknesses in individuals with FXS, treatment of medical problems, behavioral modification, and psychopharmacology for attention deficits, anxiety, or problematic maladaptive behaviors. Psychopharmacologic treatment of attention-deficit/hyperactivity disorder symptoms, anxiety, hyperarousal, and irritability or aggressive behaviors with medications such as stimulants, selective serotonin reuptake inhibitors, alpha-agonists, and antipsychotics appears to be helpful by assessment in a clinical setting in approximately 50% of patients. Response is not complete, however, and data from a national survey on FXS showed that approximately 10% to 20% of respondents thought that medication was not helpful for the behavior problems being treated in their son or daughter with FXS, whereas only approximately 40% felt the medication was helping a lot. Thus, there is clearly an unmet need in the FXS field for better agents with which to treat behavior and for any treatments that target cognitive deficits; thus, treatments that modify the underlying disorder would be a tremendous advance.

To do such treatments, it is critical to understand the functions of FMRP and the mechanisms in the brain of patients with FXS that underlie the learning and behavioral defects in the absence of FMRP. To this end, the Fmr1 knockout (KO) mouse, created in 1994, with an inactivated Fmr1 gene and no functional FMRP, has been a tremendously valuable neurobiologic model to understand the role of FMRP in neurons, identify targets for treatment, and explore effects of proposed disease-modifying agents. FMRP is an mRNA-binding protein involved in the transport, localization, and translational regulation of a subset of dendritic mRNAs. FMRP is present in a protein complex at the ribosome, where it regulates dendritic protein translation in response to synaptic activation. This regulation appears to be critical for synaptic maturation because in the absence of FMRP, both in the brain of humans with FXS and in the mouse model, dendritic spines show immature elongated morphology.

FMRP appears to regulate translation pathways activated by Group 1 metabotropic glutamate receptors (mGluR1 and mGluR5), and muscarinic (M1) acetylcholine receptors and likely has a more general function in regulation of translational activation by multiple synaptic Gq-linked receptors, including dopamine D1 receptors (reviewed in references by Berry-Kravis et al and Bagni et al; Figure 2). Activation of these receptors yields phospholipase C activation and signaling through extracellular signal-regulated kinase (ERK) and mammalian target of rapamycin (mTOR)–dependent pathways, which ultimately results in loss of FMRP repressor function at the ribosome, and a pulse of new protein synthesis. Some of the FMRP-regulated proteins, in particular STEP and Arc, are linked to α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor endocytosis and resultant expression of translation-dependent group 1 mGluR-stimulated LTD in hippocampus, as well as other receptor–activated translation-dependent forms of LTD and long-term potentiation (LTP) throughout the brain. When FMRP is absent in FXS, there is both constitutively elevated translation of FMRP target mRNAs and a loss of the protein synthesis “pulse” after mGluR stimulation (both due to loss of baseline translational repression normally imposed by FMRP). Thus, levels of synaptic proteins corresponding to a number of FMRP target mRNAs have been shown to be constitutively elevated and unresponsive to group I mGluR activation in the Fmr1 KO mouse, including MAP1B, PSD95, CaMKII, STEP, PIKE, APP, Arc, PP2A, potassium channel Kv3.1b, MMP9, and others. This dysregulated excessive dendritic protein expression results in abnormal synaptic plasticity, including enhanced mGluR–activated hippocampal and cerebellar LTD, and impaired LTP in hippocampus, cortex, and amygdala. Other consequences of excessive constitutive activation of mGluR-mediated dendritic protein synthesis are found in the Fmr1 KO mouse, including excessive internalization of synaptic AMPA receptors and abnormal epileptiform discharges. Thus, FMRP is critical both for morphologic maturation of dendritic spines and for electrophysiologic plasticity and strength of synapses. The excessive group 1 mGluR signaling in the absence of FMRP and downstream effects have been termed the “mGluR theory of...
fragile X syndrome (Figure 2), although it has become clear that molecular and signaling deficits in FXS neurons are very complex and encompass more than the mGluR pathway.\textsuperscript{14,15}

The morphologic abnormalities and synaptic plasticity deficits found in the Fmr1 KO mouse are associated with numerous cognitive, behavioral, and electrophysiologic phenotypes, including abnormal ocular dominance plasticity, olfactory learning deficits, impaired memory formation, decreased motor learning, increased open-field hyperactivity, abnormal marble burying, abnormal social behaviors, abnormal prepulse inhibition, prolonged epileptiform bursts, neuronal network hyperexcitability, audiogenic seizures, abnormal growth patterns, and increased protein synthesis.\textsuperscript{14-19} The Drosophila model of FXS, in which there is loss of dfmr (homolog of the FMR1 gene in the Drosophila genome), shows defects in circadian rhythms, synaptic branching, courtship behavior, and learning.\textsuperscript{14,15,20} The abnormal phenotypes in the mouse and fly models in many cases resemble or overlap those seen in humans with FXS.

The abnormal mGluR-activated signaling pathway activity observed in the absence of FMRP in the mouse model of FXS has led to identification of numerous possible types of treatment targets, listed in Table 2 and depicted in Figure 2,\textsuperscript{14,15} directed at (1) reduction of activity in signal transduction pathways leading from group 1 mGluRs or other Gq-linked receptors to the dendritic translational machinery; (2) reduction of activity of individual proteins regulated by FMRP; (3) increased expression and activation of surface AMPA receptors; (4) modification of activity of other receptors/proteins that regulate glutamate signaling; and (5) blocking translation of mRNAs regulated by FMRP using antisense technology. Treatments aimed at all of these categories of targets are currently in preclinical studies or clinical trials for treatment of FXS (Table). Many of these targeted treatments have shown success in reversing effects of absent FMRP in the Fmr1 KO mouse\textsuperscript{21} and dfmr fly\textsuperscript{20} models even in adulthood, suggesting that there may not be an absolute developmental requirement for FMRP and intervention to correct the synaptic dysfunction may be successful when applied in adulthood. Examples of successful preclinical testing in FXS models that has led to early proof-of-concept clinical trials and subsequent larger trials are presented in the following discussion.

Lithium is thought to reduce activity in the signaling pathway for group 1 mGluR-dependent activation of translation by attenuating GSK3β activity and possibly phosphatidylinositol turnover.\textsuperscript{22} Lithium has been shown to improve defects in naïve courtship behavior, immediate recall, and short-term memory in dfmr mutant flies\textsuperscript{20} and to reverse phenotypes, including audiogenic seizures, open field hyperactivity, deficits on a social interaction task, learning deficits, anxiety, novel object recognition, and dendritic spine shape in the Fmr1 KO mouse model.\textsuperscript{16,22} In a pilot open-label proof-of-concept lithium trial in 15 patients with FXS, significant improvement in behavior was seen in the Total Aberrant Behavior Checklist–Community Edition (ABC-C) Score, numerous ABC-C subscores, the Maladaptive Behavior subscore from the Vineland Adaptive Behavior Scale, a parent-rated visual analog scale (VAS) for target behaviors, and the clinician-rated Clinical Global Impression–Improvement scale (CGI-I). Improvement in verbal memory on the RBANS list learning task also was demonstrated in addition to normalization of abnormal ERK phosphorylation rates in lymphocytes.\textsuperscript{23} Side effects of polydipsia and polyuria were seen relatively frequently as expected, and a few participants

<table>
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<th>Preclinical</th>
<th>Early Phase 1 or 2 Clinical Studies</th>
<th>Large Phase 2 or 3 Clinical Trials</th>
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<tr>
<td>STEP inhibitor (2)</td>
<td>CX516—AMPA activator (3)</td>
<td>Arbaclofen—GABA-B agonist (4)</td>
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<td>Minocycline—MMP9 blocker (2)*</td>
<td>AFQ056—mGluR5 blocker (1A)</td>
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<td>PAK inhibitor (1B)</td>
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<td>RO4917523—mGluR5 blocker (1A)</td>
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<td>P13K Inhibitor (1B, 2)</td>
<td>Ganaxolone—GABA-A agonist (4)</td>
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<td>SLACK channel blocker (4)</td>
<td>Lovostatin—ERK inhibitor (1B)*</td>
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<tr>
<td>Endocannabanoid blocker (4)</td>
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<td>NNZ-2566—IGF-1 agonist (4)</td>
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<tr>
<td>Translation stalling agents (5)</td>
<td>Oxytocin (4)</td>
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</table>

Abbreviations: AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; ERK, extracellular signal-regulated kinase; FXS, fragile X syndrome; GABA, γ-aminobutyric acid; GSK3β, glycogen synthase kinase-3β; mGluR, group 1 metabotropic glutamate receptor; MMP9, matrix metalloproteinase-9; PAK, p21-activated kinase; P13K inhibitor, phosphatidyl inositol 3 kinase; SLACK, sequence like a calcium-activated K channel; STEP, striatal-enriched tyrosine phosphatase.

\*Numbers in parentheses indicate category of proposed targeted therapeutic agent based on location of impact on signaling pathway regulated by FMRP (see Figure 2).  
\*Drug has already been approved by the Food and Drug Administration for another indication but has been or is being tested for repurposing for FXS.
had abnormal thyroid measurements on lithium. Lithium has not been studied further in FXS because of concerns about chronic side effects and the expectation that other agents in development that work on cell surface targets such as receptors may have less off-target toxicity.

Of synaptic protein targets thought to be regulated by FMRP and overexpressed in the Fmr1 KO and, by extension, in FXS, only MMP9 has had a pharmaceutical inhibitor sufficiently well developed at present for human trials. Minocycline, an antibiotic that inhibits MMP9, was found to normalize dendritic spine phenotypes and improve anxiety and exploratory behavior in the Fmr1 KO.24 An initial open-label trial of minocycline in 20 participants older than 12 years with FXS showed behavioral improvements on the ABC-C, VAS, and CGI-I.25 Two individuals had to stop treatment because of increased antinuclear antibody levels, despite lack of signs of drug-induced lupus. A placebo-controlled crossover trial of minocycline in children ages 5 to 17 years with FXS showed improvement on the CGI-I and on a post hoc analysis of the VAS, but not in any other measures.26

A variety of GABA agonists have rescued the lethality phenotype from glutamate-containing food, as well as memory deficits and neuropathologic phenotypes in the dfmr mutant fly.27 In the Fmr1 KO mouse, racemic baclofen, a GABA-B agonist, rescues the audiogenic seizure phenotype.28 Arbaclofen, the more active enantiomer of baclofen, a GABA-B agonist, has shown promise in children with FXS aged 5 to 11 years is pending. Acamprosate, the primary outcome of ABC-FX SW. An additional phase 3 trial with FXS did not show benefits for arbaclofen over placebo in the more socially impaired subgroup (N = 27) for other measures.26

In a phase 2, double-blind, placebo-controlled crossover trial with 4-week treatment periods separated by a washout,30 arbaclofen showed no safety issues and improvement over placebo in the entire per protocol group (N = 52) on a VAS for parent-nominated behaviors and on the ABC-FX (ABC-C refactored for FXS population)11 Social Withdrawal (SW) subscale. In a post hoc analysis, arbaclofen showed improvement over placebo in the more socially impaired subgroup (N = 27) for the treatment period preference, CGI-I, V, Vineland Adaptive Behavior Scale Socialization Subscale, ABC-C SW subscale, ABC-FX SW subscale, and a responder analysis. However, a large phase 3 placebo-controlled trial in 12- to 50-year-old individuals with FXS did not show benefits for arbaclofen over placebo in the primary outcome of ABC-FX SW. An additional phase 3 trial in children with FXS aged 5 to 11 years is pending. Acamprosate, currently approved by the Food and Drug Administration for alcohol withdrawal, with agonist properties at both GABA-A and GABA-B receptors, has shown promise in children with FXS in an open-label trial31 and is to be evaluated in a placebo-controlled study beginning this year. Ganaxolone is also being evaluated in a small placebo-controlled study (clinicaltrials.gov).

Negative modulators of the mGluR5 receptor have reversed numerous phenotypes in FXS animal models. In the dfmr mutant fly, treatment with 2-methyl-6-(phenylethynyl)-pyridine (MPEP) reversed impairments in naïve courtship behavior, immediate recall and short-term memory, mushroom body formation, odor-shock memory, and survival on glutamate-containing food.14,20 MPEP and other mGluR5 negative modulators (including fenobam, AFQ056, CTEP, and STX107) have reversed multiple phenotypes, including audiogenic seizures, epileptiform bursts, open field hyperactivity, dendritic spine shape, prepulse inhibition, increased protein synthesis, exaggerated LTD, and abnormal marble burying.14-18 Fmr1 KO mice heterozygous for a null mutation in the gene coding for the mGluR5 receptor have 50% reduction in mGluR5 expression in addition to loss of FMRP and show reversal of Fmr1 KO phenotypes, including abnormal ocular dominance plasticity, increased dendritic spine density, increased basal protein synthesis, exaggerated inhibitory avoidance extinction, audiogenic seizures, and accelerated body growth.19 Fenobam, the first mGluR5 blocker used in humans with FXS, administered in a single oral dose to 12 adult males and females with FXS,13 showed a good safety profile and resulted in a significant improvement in abnormal prepulse inhibition compared with untreated control participants with FXS. Concurrently a phase 2 double-blind, placebo-controlled crossover trial of AFQ056 in 30 adult males with FXS treated for 28 days each with AFQ and placebo14 suggested improvement in maladaptive behavior on the ABC-C, CGI-I, VAS, and the Repetitive Behavior Scale, in a post-hoc analysis in the subgroup with full methylation of FMR1. This outcome was adequate to support further development of AFQ056 for treatment of FXS, with larger multinational trials ongoing. RO4917523, another mGluR5 negative modulator, is also in large multinational trials in FXS (clinicaltrials.gov).

Although many neuronal targets for treating the underlying disorder in FXS have emerged, and early translational work has begun (Table), there are still many uncertainties about how to optimally demonstrate treatment effects in a clinical trial setting.35 There are no models for disease-modifying treatment trials for FXS or any neurodevelopmental disorders. Trial design issues in FXS trials include the following: (1) dosing windows may be critical and may be different for females and mosaic males; (2) side effects may be difficult to ascertain in cognitively impaired individuals; (3) timing of treatment will likely be important because, given the extended period of brain wiring in humans compared to that of mice, treatment may work better when started in younger individuals despite the finding that phenotypes can be reversed in adult Fmr1 KO mice; (4) length of treatment needed to demonstrate measurable cognitive improvement is unknown and current trials have used behavior as primary outcomes for this reason, but trials with intensive learning or training protocols may be required to see cognitive effects of a targeted treatment; (5) best logistics including drug formulation, allowance of concomitant behavioral medications, and fixed versus adjustable dosing must be determined; (6) recruitment and travel issues can be problematic in studies of a
rare disorder in which participants may need to come to trial sites from far away (this problem is being partially alleviated by the formation of the Fragile X Clinical and Research Consortium to generate a network of Fragile X Clinics across the country at which trial sites can be housed); and (7) validated, sensitive outcome measures in FXS are lacking, and biomarkers and direct phenotype measures known to correlate with functional improvement are also lacking—only a small number of behavior rating scales such as the ABC-FX have been validated for FXS, and these are subject to large placebo effects, whereas more objective scientific measures that tap into core phenotypes (such as eye tracking for gaze aversion) lack known functional correlates and thus are not suitable to support drug approval. These trial design issues will need to continue to receive ongoing attention and work to ultimately be able to demonstrate disease modification in FXS.

There is significant overlap between pathways involved in FXS and pathways in which gene products associated with ASDs are active. The overlap falls into three broad categories for ASD genes: (1) defects in proteins in the signaling cascade for activation of FMRP-regulated translation such as SHANK, mammalian target of rapamycin (mTOR), PAK, and PTEN; (2) defects in proteins regulated directly by FMRP such as PSD95 and Arc; and (3) defects in proteins that regulate activity levels and balance of activity in brain glutamate and GABA systems. Indeed, this overlap has been recently supported by the finding that FMRP binds to one-third to one-half of all genes identified as associated with autism in a meta-analysis of exome screening studies. Treatments directed at all three of these mechanisms are becoming available in FXS trials (Table), and if successful, these treatment trials will likely be extended to cohorts with ASDs and other cognitive disorders. Progress in development of targeted treatments for FXS is likely to result in models for medical intervention to reverse central nervous system defects and resultant clinical manifestations of autism, other neurodevelopmental disorders, and intellectual disability.

References are available online at www.rush.edu/neurosciencereview.
Bacterial Infections of the Central Nervous System

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Articles of particular interest, published recently, are indicated as follows: •, of importance; ••, of major importance. Annotations are provided for these articles online.

Introduction

A broad range of bacteria affect the central nervous system (CNS). Bacterial CNS infections can be community-acquired, healthcare-associated, associated with trauma, or a continuation of systemic disease. Furthermore, the immune status affects whether certain bacteria are likely to afflict an individual.

Many patients with bacterial CNS disease require intensive care. Most patients have altered mental status, and if the mental status is impaired to the point of failure to clear secretions or maintain a patent airway, endotracheal intubation is required.1 Furthermore, many patients with CNS infections have elevated intracranial pressure (ICP) or cerebral edema and may require hyperosmolar treatment,2 ICP monitoring, or cerebral spinal fluid (CSF) drainage.3 Fever, which is also commonly present in bacterial CNS disease, may not only raise ICP but also worsen secondary brain injury.4 Therefore, relative normothermia should be achieved with antipyretics or cooling devices. Induced hypothermia has shown promising results in animal studies of bacterial meningitis but requires further study for use in patients.5

Although uncommon, both barbiturate coma6 and decompressive hemicraniectomy have been used in bacterial meningitis to control ICP.7 Other common complications of bacterial CNS infections are seizures and nonconvulsive status epilepticus in more than 25% of patients admitted to neurocritical care units,8 and therefore these patients require continuous electroencephalography and aggressive treatment to abolish seizure activity.1

Bacterial Meningitis

Bacterial meningitis remains one of the most feared diseases involving the nervous system. Despite advances in optimal antibacterial treatment, the overall prognosis remains poor, with 10% to 25% mortality and 5% to 40% of survivors suffering from significant morbidity.9,10

The incidence of community-acquired bacterial meningitis is estimated to be 3 to 6 cases per 100,000 per year in developed countries11 and is probably higher in developing countries.12

The bacteria most commonly responsible for meningitis in adults are Streptococcus pneumoniae (47%-51%), Neisseria meningitidis (25%-37%), group B streptococcus (about 15%), and Listeria monocytogenes (4%-10%).13 Other less frequent organisms include Staphylococcus aureus, coagulase-negative staphylococci, Haemophilus influenzae, Escherichia coli, and other enterobacteriaceae. The different organisms may have certain implications. Adults with a history of splenectomy or immunoglobulin deficiency are at risk of S. pneumoniae infection. Immunocompromising conditions as well as asplenia are risk factors for H. influenzae infection. Neisseria meningitidis is more common in young adults. The rate of listeria is higher in patients older than 50 years or immunosuppressed patients. Aerobic gram-negative bacilli can be found after head trauma or neurosurgical procedures, although the pneumococcus remains the most common cause of meningitis in patients with CSF leaks.

Pathogenesis

Cerebral damage results from the immune response to the microorganism rather than direct injury by the bacteria.13 A number of proinflammatory cytokines (TNF, IL-1, IL-6) are produced by endothelial cells and astrocytes after exposure to bacterial cell surface components.14 Bacteremia and cytokines lead to release of excitatory amino acids, nitrogen free radicals, and oxygen compounds, which promote brain damage. In addition, meningial inflammation promotes hyperemia of the vasculature, and the increased permeability of the blood–brain barrier in the setting of inflammation, proteinaceous substances, and leukocytes all contribute to inflammation in the CSF. This situation further augments the inflammatory cascade, leading to brain edema and neuronal injury.15 This process of brain injury can continue even after eradication of the organism.

Clinical Presentation

The classic triad of bacterial meningitis consists of fever, neck stiffness, and altered mental status. This triad, however, is only 44% sensitive. At least 2 of the 4 symptoms of headache, fever,
neck stiffness, and altered mental status are present in 95% of patients. Meningeal signs, such as neck stiffness and the Kernig and Brudzinski signs, have a sensitivity of around 50% to 60% in children but are even less reliable in adults. The average Glasgow coma scale (GCS) score on hospital admission is 10 to 11, and 10% to 20% of patients are comatose. Loss of consciousness on admission is a major predictor of outcome. If the GCS is between 3 and 8, mortality is 33%, whereas it is 10% for patients with a GCS between 9 and 12 and 0% for patients with a GCS between 13 and 15. Seizures occur in 15% to 25% of patients and are associated with a worse outcome. Apart from seizures, the most common complications are hyponatremia (25%) and acute hydrocephalus (3%-8%). Over the course of the illness, hydrocephalus develops in as many as 20% of patients. Furthermore, arterial or venous cerebrovascular complications occur in as many as 20% to 30% of patients. Abscess formation complicates meningitis in 1.5%, and of these, 57% have multiple abscesses. The acronym HACTIVE—hydrocephalus, abscess, cerebritis/cranial nerve lesions, thrombosis, infarct, ventriculitis or vasculopathy, extra-axial collection—summarizes the complications of bacterial meningitis. The most frequent cause of death is elevation of ICP.

Diagnosis

Blood should be drawn for culture immediately and definitely prior to antibiotic treatment. Blood cultures identify the organism in 50% to 80% of patients. If possible, CSF should be obtained immediately, as well. CSF is essential to establish the diagnosis, identify the organism, and undertake in vitro antibiotic susceptibility testing. Complete sterilization can occur as early as 2 hours after starting antibiotics, and CSF usually will be sterile after 8 hours. However, starting antibiotics should not be delayed if a lumbar puncture cannot be done expeditiously. Imaging prior to a lumbar puncture mainly serves to determine whether brain edema and elevated ICP with risk of herniation are present. In one series, the herniation rate in bacterial meningitis was 1%. Guidelines from the Infectious Diseases Society of America (IDSA) recommend that if a patient does not have either a history of CNS disease, new onset seizures, an immunocompromised state, or specific abnormal neurological findings, a lumbar puncture should be done immediately. If any of those features is present, blood should be drawn for culture, antibiotics should be started, and a head computed tomography (CT) image should be obtained. The opening pressure on lumbar puncture is commonly elevated. The classic CSF characteristics are a polymorphonuclear pleocytosis, hypoglycorrhachia, and elevated protein. The pleocytosis exceeds 100 cells/mm³ in 90% of patients, with a range of 100 to 10 000 cells/mm³ with 80% to 90% neutrophils. However, a lymphocytic predominance does not exclude bacterial meningitis, especially if antibiotics have been started before the sample is obtained, and the cell count may be lower in immunocompromised patients. Total protein is elevated in 90% of patients with community-acquired bacterial meningitis. Decreased CSF glucose level (< 40 mg/dL) supports a bacterial etiology. Antibiotic treatment will cause the CSF white blood cell (WBC) count to decrease in 48 to 72 hours, with a rise in the proportion of mononuclear cells, as well as attenuate the hypoglycorrhachia. A high CSF lactate concentration may have better accuracy in favoring bacterial over aseptic meningitis than CSF WBC count, glucose, and protein; however, it loses sensitivity once antibiotic treatment is started (98% vs 49%) and is less accurate in patients with coexisting CNS disease such as stroke or traumatic brain injury. Gram stain is positive in 69% to 93% of patients with pneumococcal meningitis and is positive in 30% to 89% of those with meningococcus. CSF cultures are positive in 80% to 90% of patients with acute community-acquired bacterial meningitis when blood for culture is drawn prior to initiation of antimicrobial treatment.

CSF cortisol, heparin-binding protein, IL-6, IL-12, IL-1b, TNF-a, complement component B, complement component 3, and soluble triggering receptor expressed on myeloid cells have been studied as markers for acute bacterial meningitis in single studies, most of which have included fewer than 40 patients and therefore are of limited generalizability. For differentiation of aseptic from bacterial meningitis, complement component B has been found to have 100% sensitivity and specificity in adults, and complement component 3 and heparin binding protein are excellent as well. In pediatric patients, serum C-reactive protein and procalcitonin are highly discriminatory between bacterial and viral meningitis.

Management

Empirical antibiotics should be based on local epidemiology, the patient’s age, and the presence of underlying diseases or risk factors and should be instituted without delay. A typical regimen in the United States consists of meningitic doses of a third-generation cephalosporin to cover pneumococcus and meningococcus plus vancomycin to cover resistant pneumococcus, with or without ampicillin to cover Listeria; acyclovir is also often added initially to cover herpes simplex virus. Mortality increases sharply with delay in antibiotic treatment, with a case fatality of 5% to 6% when antibiotic treatment is given within 6 hours, up to 45% after 6 to 8 hours, and 75% after 8 to 10 hours. Delay in antibiotic treatment longer than 3 hours after arrival at the hospital also has been found to be associated with increased 3-month mortality. The duration of antibiotic therapy depends on the organism, the severity of disease, and the agent used. The World Health Organization recommends at least 5 days of treatment in nonepidemic situations or if fever, coma, or convulsions persist for longer than 24 hours. Many authorities in higher-income countries recommend at least 7 days of treatment for H. influenzae and meningococcal meningitis and 10 to 14 days for pneumococcal meningitis. Lack of clinical response after 24 to 48 hours indicates treatment failure, and a repeat lumbar puncture should be performed to determine the degree of resolution of hypoglycorrhachia and reduction of CSF lactate, which are the earliest indicators of improvement.

Adjunctive Agents

Corticosteroids are the most widely studied adjunctive therapy in bacterial meningitis. Besides steroids, agents studied as adjunctive...
therapy include glycerol, antiepileptic medications, activated protein C, plasma exchange, intravenous immunoglobulin (IV Ig), caspase inhibitors, antioxidants, poly-ADP-polymerase inhibitors, and metalloproteinase inhibitors, but none of these is currently recommended. Corticosteroids inhibit the synthesis of proinflammatory cytokines, stabilize the blood–brain barrier, and reduce ICP. Dexamethasone has excellent CSF penetration. It is given at 10 mg intravenously 15 to 20 minutes before or with the first dose of antibiotics and then continued every 6 hours for 4 days. The effect of dexamethasone depends on the bacterial species and the age of the patient. A meta-analysis including 5 double-blinded, randomized controlled trials since 2001 comparing clinical outcomes showed that dexamethasone and placebo are comparable for death, severe neurological sequelae, and bilateral deafness, but there is reduced hearing loss among survivors who received dexamethasone (odds ratio [OR], 0.77). In HIV-negative patients, dexamethasone reduces the likelihood of death or severe neurological sequelae (OR, 0.68); however, there is no effect in children or HIV-positive patients. The totality of evidence therefore suggests that corticosteroids may be beneficial in adult HIV-negative patients with definite bacterial meningitis in higher-income countries. The IDSA practice guideline recommendation lists dexamethasone as beneficial in adult HIV-negative patients with definite bacterial meningitis and treatment of bacterial meningitis, there are no data from randomized controlled studies evaluating ICP monitoring. and treatment of bacterial meningitis, there are no data from randomized controlled studies evaluating ICP monitoring. Although elevation of ICP may pose a problem in the course of meningitis, the clinical benefit of dexamethasone has not been found to prevent meningitis.47 Prophylactic use of antibiotics in basilar skull fracture with or without CSF leak has not been found to prevent meningitis.47

Other Considerations
Although elevation of ICP may pose a problem in the course and treatment of bacterial meningitis, there are no data from randomized controlled studies evaluating ICP monitoring. Retrospective data showed that ICP is overall higher in nonsurvivors.41 Similarly, clinical data are lacking for hypothermia. Vaccines to prevent bacterial meningitis are currently available for H. influenzae, S. pneumoniae, and N. meningitides.42

Meningitis Associated With Head Trauma
The incidence of meningitis in moderate to severe head injury is 1.4%43 but is as high as 2% to 11% in patients sustaining open compound injuries.44 Basilar skull fracture and CSF leak increase the risk of meningitis. The median time between injury and onset of meningitis is 11 days.45 Empirical treatment for meningitis in the setting of penetrating head injury or basilar skull fracture consists commonly of vancomycin combined with a fourth-generation antipseudomonal cephalosporin or a carbapenem.46 Prophylactic use of antibiotics in basilar skull fracture with or without CSF leak has not been found to prevent meningitis.47

Brain Abscess
Brain abscesses can arise through spread of a contiguous infection through the valveless diploic veins; from the oropharynx, middle ear, or sinuses; or hematogenously, such as from lung abscess, endocarditis, intra-abdominal abscess, or even a urinary tract infection.48 Trauma was the most common cause (33%) in a large South African series.49 Risk factors for brain abscess include diabetes mellitus (20%), malignancy (17%), liver cirrhosis, HIV infection, and heart disease.50 Abscess formation begins as a localized area of cerebritis and develops into a collection of pus surrounded by a well-vascularized capsule within approximately 14 days.

Organisms depend on the source. Brain abscesses can rupture into the meninges and present as meningitis, in which case the culprit often is S. viridans or S. aureus from a seeding endocarditis.24 If the abscess is a consequence of community-acquired meningitis, the microbiology corresponds to that of the meningitis.24 However, brain abscess in patients with meningitis is quite rare; exceptions include Citrobacter diversus and Elizabethkingia meningoseptica in neonates and Enterobacter cloacae in older patients. Pus in the intraventricular space usually results from rupture of intraparenchymal abscess. A few cases of a true intraventricular brain abscess, in which the intraventricular pus is contained in a capsule, have been reported. In these patients, the abscess evolved from adjacent cerebritis or ventriculitis from iatrogenic seeding or seeding via the hematogenous or CSF route. A possible underlying anatomical abnormality to facilitate trapping has been suggested.24 A source of the infection can be found in 42% to 57% of patients, depending on the series.50,53 In one series, 41% of infections had a distant focus, 23% were operation related, 22% were due to a contiguous infection, and 14% were meningitis related.50 In other series, an identifiable source was found in 57% of infections. Multiple abscesses are found in 1.9%.51 The reported percentage of identified organisms ranges from 53% to 70%.50,53 Common organisms are enterobacteriaceae (21%; Klebsiella most commonly), streptococcal species (20%), or mixed microbiology (18%).52 In meningitis-related abscess formation, the rate of multiple abscesses is as high as 57%.24 When the etiology is trauma, the most common organisms are S. aureus and S. epidermidis.49 Males are more commonly affected than females in most series. The clinical presentation depends on site, size, number of lesions, and the presence of secondary cerebral injury. Symptoms of infection often are not obvious. Fever occurs in 24% to 70% of patients.44 Altered consciousness (55%) and headache (40%) are common features,42 as are vomiting or seizures (49%).51 Abscess location is hemispheric in 80% of patients, with the frontal lobes being more commonly affected than the parietal and temporal lobes. The basal ganglia are affected in 14%, and the cerebellum is affected in 7%.50 If the location is cerebellar, the etiology is mastoiditis in 69%.49

Factors that have been shown to predict outcome include GCS on presentation, immunodeficiency, or underlying disease,23 as well as the size of the abscess.46 The most successful predictor of outcome seems to be the extent of neurological compromise on presentation.49 Further predictors of mortality are etiology, presence of papilledema, neurological deterioration, preoperative hydrocephalus, focal deficit, aural discharge, and stereotactic surgery as opposed to larger surgical access.49 Imaging usually forms the basis of diagnosis. If CSF is obtained, pleocytosis can be found in 66% of patients.52 Indications for medical treatment
alone are multiple abscesses, abscess location in a high-risk region of the brain, and concomitant endocarditis. The ideal empirical antibiotic regimen includes antibiotics that are active against the suspected infecting flora, can penetrate the brain tissue and intracranial pus, have a good long-term safety profile, and can be administered both intravenously and orally. The advantage of conservative treatment is the avoidance of morbidity linked to a surgical procedure such as brain edema, hemorrhage, or spread of the infection. Patients with bacterial morbidity linked to a surgical procedure such as brain edema, hemorrhage, or spread of the infection. The mortality usually has been reported around 11% to 13% of patients but depending on etiology can range from 8% to 53%. Good outcomes have been reported in up to 81% of patients. Seizures are the most common residual morbidity. For abscesses with intraventricular extension, mortality is much higher, up to 80%.

CNS Infections Associated With Procedures or Devices

Nosocomial CNS infections are a growing concern in critical care medicine. The etiology is different from that of community-acquired infections. Bacterial CNS infections may result from invasive neurological procedures such as craniotomy, dural puncture, spinal anesthesia, or placement of a temporary or permanent intracranial or intraspinal device. The clinical presentation varies with the underlying process and extent of disease, but often is nonspecific and includes fever and decreased level of consciousness. Specific organisms depend on pathogenesis, predisposing factors, and hospital prevalence of organisms. Neurosurgical procedures or CSF shunts are commonly associated with coagulase-negative staphylococci, S. aureus, aerobic gram-negative bacilli, or Pseudomonas species. In the presence of a CSF leak, organisms that colonize the nasopharynx, especially S. pneumoniae, will be found, as well as staphylococcal species and gram-negative bacilli.

Craniotomy

Infections after craniotomy include meningitis, bone flap infection, epidural abscess, brain abscess, and subdural empyema. The incidence of postcraniotomy meningitis was 6% in a recent large series, but numbers may vary depending on characteristics of the surgical center and location. In another series the incidence of bacterial meningitis was found to be 0.8% to 1.5%. Staphylococcus species are the culprit in 37% of infections after neurosurgical procedures, and aerobic, gram-negative species (especially Enterobacteriaceae) account for up to 33%. Repeat resections for gliomas, procedures traversing areas of bacterial colonization such as the paranasal sinuses, a concomitant infection at the site of incision, or duration of surgery longer than 4 hours predispose patients to postcraniotomy infections. One-third of infections manifest during the first week after surgery, one-third manifest during the second week, and one-third manifest after the second week. Preventive measures include surgical technique and prophylactic antibiotics to achieve adequate tissue concentrations prior to incision and for up to 24 hours postoperatively. Diagnosis is made on the basis of imaging, or aspirate or CSF analysis. CSF cell count, however, has low sensitivity and specificity. The interpretation is particularly difficult in the presence of aseptic meningitis, intraventricular or subarachnoid hemorrhage, or postoperative breakdown of the blood–brain barrier. No single CSF value is diagnostic, but CSF lactate may have the biggest utility: for bacterial meningitis after neurosurgery, a CSF lactate of greater than 4 mmol/L is 88% sensitive and 98% specific for the diagnosis of bacterial meningitis.

Infections Associated With External Ventricular Drains and Ventricular Shunts

Infections Related to External Ventricular Drains

The incidence of ventriculitis and meningitis related to external ventricular drains (EVDs) ranges from 0% to 22%, but varies depending on the definition of infection and the clinical setting. In one large series of more than 5 000 EVD insertions, the rate of positive CSF cultures was 8% per EVD placement. Risk factors for EVD-related infections (EVDRLs) and EVD management include CSF leak from the EVD site, EVD irrigation, frequent CSF sampling, and EVD reinsertion due to malfunction. Furthermore, the presence of a depressed skull fracture and a severe underlying illness carry a higher risk. In older series, intraventricular and subarachnoid hemorrhage were found to pose a higher risk for EVD infection, but this finding has not been confirmed in more recent series. The duration of the EVD similarly seems to bear risk, but the results are conflicting. Although in some studies an increase in EVDRL was found as early as 5 days after placement, in other series a peak on day 10 was found with no increase thereafter. The lack of progressive increase in the infection rate after 10 days suggests that the insertion technique is of particular importance.
The widely used definition of EVDRI by the Centers for Disease Control and Prevention (CDC) and the National Healthcare Safety Network requires organisms in CSF culture, at least 1 fever (>38°C), headache, stiff neck, meningeal signs, cranial nerve signs and irritability, and at least 1 of the following: CSF abnormality (pleocytosis, elevated protein, hypoglycorrhachia), organisms on CSF gram stain, organisms in blood culture, a positive antigen test (of CSF, blood, or urine), or a diagnostic antibody titer and antibiotic treatment if diagnosis is made antemortem. The criticisms of this definition are that it does not distinguish between infection, colonization, and contamination. Furthermore, the clinical criteria are controversial because neurosurgical patients often have aseptic meningitis, and assessing signs of meningitis in critically ill patients may be unreliable or impossible. A differentiation between contamination, colonization, and infection was proposed by Lozier et al., with contamination defined as isolated positive CSF culture (and/or gram stain) plus CSF glucose, protein, and cell count in the expected range; colonization was defined as repeated positive CSF cultures (and/or gram stain) with normal CSF profile without clinical symptoms except fever. EVDRI is characterized by progressively lower CSF glucose, rising CSF protein, and rising CSF pleocytosis with 1 or more positive CSF cultures (and/or gram stain). However, the definition of abnormal CSF in the setting of CNS disease is difficult. CSF cell count, glucose, and protein concentrations in patients with EVDRI are very similar to those of patients without infections, such that there is no single significant diagnostic or predictive value among commonly used CSF parameters. The cell index ([CSF leukocytes/CSF erythrocytes]/[serum leukocytes/serum erythrocytes]) has been found to be predictive of EVDRI ahead of conventional methods. A CSF lactate level greater than 4 mmol/L has been found to be associated with CSF infection in patients with intraventricular hemorrhage and EVD, but these markers have not been validated in general. Organisms of the skin flora are the most common pathogens, but gram-negative pathogens are increasingly found. Fungi account for only a small fraction. Few controlled clinical trials have been undertaken to study the optimal management of EVDRI. The antibiotics chosen must be active against the most likely organisms and achieve adequate CNS concentration. Because of the high prevalence of nosocomial staphylococci, vancomycin is routinely used.

Because of the rising frequency of gram-negative infections, an antipseudomonal cephalosporin or carbapenem should be added initially. In the case of vancomycin intolerance, vancomycin failure, or vancomycin-resistant enterococcus, linezolid can be used as an alternative. Although optimal treatment for fungal EVDRI remains uncertain, most EVDRIs are confined to the CSF, and fluconazole or voriconazole achieve the best CSF levels. Currently no antibiotics are approved for intrathecal use by the Food and Drug Administration, and no consensus exists among the medical community on indications for intrathecal treatment. However, intrathecal vancomycin has been successfully used to treat MRSA, gentamicin has been used to treat gram-negative pathogens, daptomycin has been used to treat Enterococcus faecalis, and colistin has been used to treat multi-drug-resistant (MDR) Acinetobacter. Therefore, intrathecal therapy may be considered for severe ventriculitis, persistently positive CSF cultures despite appropriate intravenous dosing, MDR pathogens, or intolerance of systemic antibiotic administration or when device removal is not feasible. No evidence-based guidelines exist regarding the importance of device removal and duration of antimicrobial therapy. On the basis of the literature for vascular catheter-related bloodstream infections, immediate EVD removal or exchange is recommended. EVD maintenance may be considered in hemodynamically stable patients with minimal CSF abnormalities and cultures growing coagulase-negative staphylococci, if the duration of catheterization is anticipated to be short (<3 days) and placement of an internal shunt is not anticipated. After the device has been removed and cultures return negative, treatment for 10 to 14 days is usually recommended.

**Infections Related to Permanent CSF Shunts**

CSF shunt placement can either be primary (without prior history of neurosurgical procedures) or secondary (as internalization of an EVD). Infection rates are overall similar to that of EVDs, with higher rates after secondary shunt placement. The typical CSF shunt consists of a proximal segment entering the lateral ventricle and a distal segment terminating in the peritoneal, pleural, or vascular space. Besides ventriculitis or meningitis, infection patterns depend on the location of the distal segment, and shunt-related infections may manifest as bloodstream infection, pleuritis, or peritonitis solely. The incidence of meningitis after placement of a ventriculoperitoneal shunt ranges from 4% to 17%. Most commonly, the catheter is colonized at the time of insertion, and the majority of infections occur within 1 month of surgery. Diagnosis is largely based on a combination of clinical and CSF findings, similar to the diagnosis of EVDRI. CSF lactate is not usual a good indicator for CSF shunt infections. Treatment of CSF shunt infections is similar to that of EVDRI, with a usual initial empirical regimen of vancomycin and antipseudomonal cephalosporin or carbapenem, depending on local microbiological patterns. In addition to systemic antibiotics, intraventricular antibiotics, most commonly vancomycin and gentamicin, have been used empirically in treating CSF shunt infections. Despite lack of Food and Drug Administration approval for intrathecal therapy, it has played an important role in the treatment of Acinetobacter meningitis because of the high required minimally inhibitory concentrations. In addition, immediate removal of the shunt in its entirety and EVD placement seem most effective. Studies on duration of antimicrobial therapy and optimal timing of shunt replacement are few and depend on the organism. According to the IDSA guidelines on bacterial meningitis, patients with shunt infections due to coagulase-negative Staphylococci with normal CSF findings can be reshunted 3 days after removal if the CSF cultures after removal are negative, after 7 days of antibiotic treatment in the setting of abnormal CSF and negative repeat cultures, or after 10 days of culture negativity in the setting of initially positive repeat CSF cultures. For infections with S. aureus, gram-negative
organisms, or fungi, 10 to 14 days of antibiotic treatment and negative cultures are recommended. With combined antibiotic therapy, treatment is successful in more than 85% of patients.

Prevention of EVDR and Shunt Infections

The introduction of bundled payment in the US healthcare system has led to a decrease in healthcare-associated infections, such as central line–related bloodstream infections. The same concept of increased awareness, standardized protocols for procedure and device maintenance, and development of a diagnostic and therapeutic algorithm for suspected device-related infection has been applied to the placement and maintenance of EVDs with a significant reduction in EVDRI, from 9.9% to 4.6% in one series. Two recent studies evaluating the periprocedural use of cephalosporins showed no benefit in preventing EVDRI, and studies comparing periprocedural with prolonged prophylaxis showed conflicting results with either no benefit or an overall decrease in infectious complications but increases in MRSA and Candida infections with a higher mortality rate. A Cochrane review showed that overall the use of preventive antibiotics is associated with a significant decrease in catheter infection (OR, 0.52), and all available data indicate that periprocedural prophylaxis may be considered, whereas prolonged use of prophylactic antimicrobials should be avoided.

For the placement of a permanent CSF shunt, no standard guidelines for the use of antimicrobial prophylaxis have been established. Practice is commonly based on clinical experience and institutional policy. Furthermore, antibiotic-impregnated catheters (with or without periprocedural systemic prophylaxis) appear to be an effective option. Minocycline/rifampin-impregnated catheters have been shown to result in reduction of infection from 9.4% to 1.3% as well as a significant reduction in catheter colonization. A second type of catheter, impregnated with clindamycin/rifampin, seems similarly efficacious. The most convincing data on the benefit of antibiotic-impregnated catheters stem from a longitudinal study showing a significant decrease in the infection rate from 6.7% to 1% after implantation of clindamycin/rifampin-impregnated ventricular catheters along with standardized protocols, but without significant change in the infection rate after initial implementation of the standardized protocol alone.

A Cochrane review has also shown an overall reduced infection rate with common gram-positive organisms with the use of antibiotic-impregnated catheters (OR, 0.21). Concerns with antibiotic-impregnated catheters include the possibility that CSF cultures could be falsely negative and drug resistance could develop. Newer options such as silver-impregnated catheters, which would not pose such problems, have also been shown to reduce the number of positive CSF cultures, colonization of the catheter tip, and CSF pleocytosis compared with standard catheters (18.9% vs 33.7%) and may become a better option in the future.

Infections Related to Lumbar Puncture and Lumbar Drains

Data are very limited on infections related to lumbar puncture and lumbar drains. Infectious complications after lumbar puncture are reported to be extremely rare, with an incidence of 1 in 50,000, mostly after spinal anesthesia and myelography. An external lumbar drain has been reported to lead to meningitis in 0% to 25.6% of patients, with the risk being highest after subarachnoid or intraventricular hemorrhage and if disconnection of the draining system occurs or if other infections are present.

Infections Related to ICP Monitors

Parenchymal ICP monitors are not commonly associated with clinically relevant infections. The largest published series included 1000 patients with no clinically significant infections, and rates found in smaller series varied from 0% to 3%. If they occur, they mostly are superficial site-entry infections. Infections of a devascularized bone flap have also been reported. If monitor tips are sent for culture, the rates of positive returns have been much higher than the actual rate of clinical infections, between 8.5% and 17%. The predominant organism was S. epidermidis (83% in one series, 48% in another series). Other organisms reported included E. coli in 20% and Corynebacterium in 11% of patients. There was no difference in culture results if patients received 1 or more monitors or whether the monitor was placed when the patient was in the operating room or the intensive care unit.

Prophylactic antibiotics were not used in these studies. One study using prophylactic antibiotics showed a culture-positive rate of monitor tips of 9.5%, and in another study evaluating the use of prophylactic antibiotic use, antimicrobial prophylaxis not only failed to reduce the infection rate but also was associated with twice as many infectious complications and a significant increase in MDR pathogens. A serious infectious complication of brain abscess formation associated with an ICP monitor was reported by Morton et al. Possible risk factors suggested by the authors included emergent monitor placement in the emergency department as opposed to an operating room or intensive care unit setting, the insertion of a second catheter through the same track, and high-dose steroid treatment for airway management while the ICP monitor is in place.

Infections Related to Deep Brain Stimulators

Deep brain stimulators (DBSs) are mostly implanted for the treatment of movement disorders or chronic pain. DBSs consist of an implanted pulse generator, a lead, and an extension. Infections usually involve the pulse generator, the connector site, or the scalp entry site. Intracranial abscess formation has also been reported but is less common. The majority of DBS-related infections are caused by skin flora, most commonly S. aureus, S. epidermidis, P. acnes, and less frequently gram-negative organisms and Mycobacterium fortuitum. The incidence of
infection related to DBSs varies from 0.62% to 14.3%, depending on the definition and inclusion criteria for infection, the patient population, and the surgical center. Treatment strategies vary, and the decision to remove a device in part or entirely, or to treat the infection with antibiotics alone, depends on the severity of the infection and institutional practice. Similarly, the duration of antibiotic treatment depends on the location and severity of the infection. For skin or soft-tissue infection, 2 weeks of antibiotic treatment is usually sufficient, whereas any conservative treatment of infections at the connector site or burr hole is likely to fail, and device removal is required because of involvement of the intracranial lead in nearly all cases, as is an extended (4- to 6-week) course of antibiotics. In case of an abscess formation, immediate removal of the entire system, followed by an extended and surgical techniques have been suggested as possible risk factors. Treatment strategies vary, and the decision to remove a device in part or entirely, or to treat the infection with antibiotics alone, depends on the severity of the infection and institutional practice. Similarly, the duration of antibiotic treatment depends on the location and severity of the infection. For skin or soft-tissue infection, 2 weeks of antibiotic treatment is usually sufficient, whereas any conservative treatment of infections at the connector site or burr hole is likely to fail, and device removal is required because of involvement of the intracranial lead in nearly all cases, as is an extended (4- to 6-week) course of antibiotics. In case of an abscess formation, immediate removal of the entire system, followed by an extended course of antibiotics, is necessary.

Although specific measures for DBS infection prevention are not established, adherence to strategies to prevent surgical site infections and perioperative antibiotics are recommended.

Tuberculous Meningitis

Tuberculosis (TB) is second to human immunodeficiency virus (HIV) as an infectious cause of death worldwide. In the United States, TB is more prevalent in adults, especially among certain high-risk groups, including the homeless, nursing home residents, ethnic minorities, and persons infected with HIV. Of patients with symptomatic pulmonary TB, 5% to 10% develop CNS disease, most commonly meningitis. About 10% of all patients with TB have CNS TB. In 38% of patients with CNS TB, concomitant extraneural TB is present. The effectiveness of the BCG vaccine for prevention of tuberculous meningitis is not established. Severity and prognosis of TB meningitis in BCG-vaccinated adults does not seem to differ from those in nonvaccinated adults.

Clinical Presentation

The average duration of illness before presentation varies widely, ranging from 11 to 72 days. In a patient presenting with a symptom duration of more than 5 days, the diagnosis of TB meningitis becomes more likely.

The time between symptom onset and presentation is less than 1 week in only 7% of patients, 1 to 3 weeks in 57%, and more than 3 weeks in 36%. The most common symptoms are similar to those of bacterial meningitis, with headache in 86%, nausea/vomiting in 64%, altered mental status in 59%, and stiff neck in 88%. Patients with TB meningitis have fever, headache, or meningismus and are more likely to have an altered mental status. Because of a predilection for the basilar meninges, cranial nerve involvement occurs in 20% to 30% of patients, most commonly affecting cranial nerves VI, III, VII, and VIII. TB meningitis can be complicated by hydrocephalus, tuberculomata, brain abscess formation, and disorders of sodium and water metabolism (such as central diabetes insipidus, SIADH, salt wasting). Stroke occurs in up to 60% of patients and is mostly ischemic. Exudates may also cause infarction through vasculitis, vasospasm, and/or proliferative intimal disease.

Diagnosis

TB meningitis is difficult to diagnose. Demonstration of acid-fast bacilli in CSF either by Ziehl-Nielsen smear or culture has remained the gold standard of diagnosis. However, sensitivities are only 10% to 60% and less than 50% (mostly 25% to 27%), respectively, and results take 2 to 6 weeks of incubation. Therefore, in practice a combination of clinical criteria, CSF evidence, imaging, and acid-fast bacilli at other sites is used to make a provisional diagnosis. The initial cornerstone is the CSF analysis. Opening pressure is usually moderately elevated (18-30 cm H2O), CSF glucose is often depressed (< 40 mg/dL), and CSF protein is usually elevated. Acellular CSF profiles may occur. If available, newer polymerase chain reaction (PCR) assays have improved the diagnostic process in TB meningitis with a sensitivity of 76% and a specificity of 89%. Another PCR test, called GeneXpert (Cepheid), has a turnover time of only 2 hours, with a sensitivity of 56% and a specificity of 98%. Imaging may reveal hydrocephalus, tuberculomata, or meningeal enhancement, but 25% of head CT scans performed at the time of initial presentation are normal. Magnetic resonance imaging (MRI) is more sensitive and can show basal exudates, infarcts, smaller tuberculomata, and/or abscesses.

Treatment

TB meningitis is difficult to treat because of drug resistance, and optimal dose and duration and composition of treatment have not been determined. Because of the high mortality and complication rate of untreated infection, patients with suspected TB CNS disease should be given antimicrobial therapy upon presentation, while awaiting diagnostic results. Treatment regimens are largely based on those for pulmonary TB, with a combination of rifampin, isoniazid (INH), pyrazinamide, and streptomycin or ethambutol for 3 months in the active phase, followed by at least 6 months of rifampin and INH. INH has been a mainstay of TB therapy since its introduction. It has activity against extracelullar and intracellular organisms, works in an organism’s growing and resting stages, and attains CSF concentrations far exceeding the minimum inhibitory concentration for susceptible organisms. The chief toxicities of INH are hepatic and neurological; concomitant pyridoxine can prevent the neurological side effects. In case of allergy or severe toxicity, other agents with high CSF penetration and favorable CSF pharmacokinetics that can be considered are ethionamide or fluoroquinolones. If an isolate of M. tuberculosis is susceptible to all drugs tested in vitro, the latest US multisociety guidelines recommend an additional 7 to 10 months of INH and rifampin after the initial 2-month multidrug regimen. Drug resistance is a large and growing problem. MDR TB is defined as resistance to at least rifampin and INH. When resistance is found, the patient...
stroke, seizures, hyponatremia, cranial nerve involvement, CSF severity of TB meningitis on presentation, and the occurrence of factors are the length of delay in treatment initiation, the MDR TB has been suggested. In addition, the use of Continuation of therapy for up to 24 months in patients with should be given at least 2 drugs that the agent is susceptible to. Intra-/intrathecal therapy in the setting of drug resistance has been described in case reports. The use of corticosteroids as adjunctive treatment has been widely studied. Although trials vary regarding severity of disease and treatment regimens, no trial has demonstrated significantly worse outcomes with the use of adjunctive corticosteroids in patients with TB meningitis, and most data suggest earlier clinical improvement, fewer neurological sequelae, and/or improved survival. A Cochrane review noted an overall decreased risk of death (relative risk [RR], 0.78) in patients with TB meningitis who received adjunctive corticosteroids, and significant benefit in terms of mortality and disabling residual neurological deficit (RR, 0.82). It is generally felt that initiation of combination antiretroviral therapy (cART) for HIV infection should be deferred until after 8 weeks of TB treatment, rather than starting immediately, in an attempt to reduce the risk of immune reconstitution inflammatory syndrome. The role of aspirin in patients with a stroke secondary to TB meningitis remains to be determined.

**Outcome**

Morbidity and mortality are considered to be dependent on the severity of the inflammatory response. Mortality has been reported to be 1 in 4 among HIV-negative adults and much higher among HIV-positive adults (67%). Major prognostic factors are the length of delay in treatment initiation, the severity of TB meningitis on presentation, and the occurrence of stroke, seizures, hyponatremia, cranial nerve involvement, CSF cell count and lactate level, HIV coinfection, and multidrug resistance. Further factors indicating a poor prognosis include extremes of age, the presence of hydrocephalus, and advanced stage of illness at presentation. Early intervention for hydrocephalus in patients with a better grade is associated with better outcome. In one series, 51% of patients with TB meningitis had died by 5 years. Of the survivors, 26% were found to have a good outcome, 16% had intermediate disability, and 7% were severely disabled.

**CNS Nocardiosis and Nocarda Brain Abscess**

Nocardia is an opportunistic pathogen that can cause disseminated disease mainly in patients who are immunosuppressed, such as those who have undergone organ transplantation or who have severe autoimmune disease, advanced HIV infection, hematological malignancies, or long-term corticosteroid use. Nocardia is a rare infection, and the literature is limited mostly to case reports and smaller series. In the largest series, reviewing 131 patients and the literature from 44 years, 34% of patients with CNS nocardiosis were known to be immunosuppressed, but other sources estimate that more than half of the patients with CNS disease are immunocompromised. CNS nocardiosis accounts for 2% of all cerebral abscesses. In patients with systemic nocardial infection, 15% to 44% of brain abscesses are caused by Nocardia. In patients with cerebral nocardiosis, nocardial infection outside the CNS occurs in up to 71%. With the increase in number of immunocompromised patients due to advances in organ transplantation and chemotherapy, as well as the emergence of treatment for HIV infection and AIDS and its aggressive use, Nocardia has become a significant opportunistic infection. Nocardiosis usually arises from direct inoculation of the pathogen through the skin or inhalation. Seeding into the CNS can follow hemogenetically from any focus. Nocardia asteroides is responsible for approximately 80% of noncutaneous invasive disease and for most systemic and CNS involvement. Nocardia farcinica, N. nova, N. brasiliensis, N. otitidiscaviarum, and N. transvalensis can also cause human infection. Nocardia farcinica is important because it mostly occurs in immunocompromised patients and is associated with higher risk of dissemination, antibiotic resistance, and therefore a higher mortality rate. The clinical presentation can vary, and nocardiosis may present as meningitis, diffuse cerebral infiltration without localization, cerebral abscess, or granuloma. Abscesses are supratentorial in 57% and infratentorial in 11% of patients; they occur as a single abscess in 54% and as multiple abscesses in 38%. The main presenting symptoms are a focal neurological deficit in 42%, seizures in 30%, and nonfocal findings such as meningeal symptoms or altered mental status in 28%. Nocardia may not be readily identified, and it has been reported to mimic a necrotic or infected tumor. Treatment options include antimicrobial therapy alone, stereotactic aspiration and biopsy, or craniotomy and enucleation. Because of the rarity of the disease and the limited number of published reports, optimal therapeutic regimens are not clearly established. The most active oral agents against N. asteroides are sulfonamides, minocycline, and amoxicillin. The therapy of choice is trimethoprim/sulfamethoxazole (1:5; 15-20/75-100 mg/kg) because of its good pharmacokinetics and CSF penetration. Parenteral antibiotics that can be used include amikacin, imipenem, ceftriaxone, and cefotaxime. The duration of parenteral therapy should be adjusted to the clinical and radiographic response and should probably be at least 6 weeks. Patients should be treated for 1 year and monitored for at least a further year after completion of therapy. For patients requiring ongoing immunosuppressive treatment, prolonged therapy and indefinite low-dose prophylaxis should be considered. It has been suggested that in a nonimmunocompromised patient with nocardial infection outside the CNS, a brain abscess smaller than 2 cm can initially be treated nonsurgically. If the clinical condition deteriorates or the abscess does not shrink within 1 month, the abscess should be aspirated. All abscesses greater than 2.5 cm should be aspirated, regardless of immune status. This approach is more aggressive than that for brain abscesses of other etiologies but is based on the characteristic thick walls, multiloculation, and tumor-like appearance, which point to atypical infections and neoplasms. Repeated aspiration may be necessary in patients with an insufficient response. The outcome is dependent on site, extent of disease, and underlying patient factors. In the review series reported by Mamelak et al, mortality was 20% in immunocompetent patients and was 55% in...
immunocompromised patients.\textsuperscript{142} Mortality may also vary with type of management and may have decreased over recent years because of earlier recognition with neuroimaging.\textsuperscript{142}

**Syphilis**

**Epidemiology**

Syphilis is a sexually transmitted disease caused by the spirochete bacterium *Treponema pallidum*. After a dramatic reduction in incidence following the introduction of penicillin, syphilis rates began to rise again, with an increase in incidence of 54\% from 2001 to 2006, reaching 4.5 cases per 100 000 by 2008. The steepest increase has been among men and women between 15 and 24 years of age.\textsuperscript{156} More than 60\% of new cases of syphilis are in men who have sex with men.\textsuperscript{156} The coinfection rate with HIV is as high as 60\%.\textsuperscript{117} The primary mode of transmission is sexual contact, through contact with infectious lesions.\textsuperscript{156} The bacterium invades through compromised skin or mucosa. Unlike other sexually transmitted diseases, syphilis not only is transmissible by vaginal or anal intercourse but also can be transmitted by oral contact with an infectious lesion.

Transmission risk among sexual partners varies from 10\% to 60\%. It is highest during early syphilis and decreases during late or latent stages of syphilis.\textsuperscript{156} Transmission can also occur in utero or through blood transfusions from a donor with syphilis.

**Clinical Presentation**

Once acquired, syphilis passes through a series of 4 overlapping stages, referred to as primary, secondary, latent, and tertiary syphilis, which are characterized by unique clinical manifestations. Comprehensive discussion of the stages of syphilis is beyond the scope of this article, and the reader is referred to the specified references.\textsuperscript{158,159} Primary syphilis usually manifests after an incubation period of 3 to 90 days with a chancre and local lymphadenopathy at the site of inoculation. The most common manifestation of secondary syphilis is a rash of varying severity. Additionally, alopecia, pharyngeal inflammation, condyloma lata, genital lesions, and nonspecific symptoms such as malaise may occur. Latent syphilis occurs between the disappearance of secondary syphilis symptoms and the appearance of tertiary syphilis. Patients are seroreactive but asymptomatic. Tertiary syphilis is characterized by long-term complications of the disease, as a late benign form, cardiovascular syphilis, or neurosyphilis. During this stage, syphilis is not transmissible. Complications of the disease are more frequent in men than in women.\textsuperscript{159}

**Neurosyphilis**

Neurosyphilis is any involvement of the CNS by syphilitic infections at any stage. All forms of neurosyphilis result from invasion of *T. pallidum* into the CNS, which usually occurs within the first few months or years of infection.\textsuperscript{160} Once the CSF is invaded, different outcomes are possible. The CNS infection may resolve spontaneously, but asymptomatic neurosyphilis occurs in 8\% to 40\% of infected individuals. Alternatively, syphilitic meningitis may follow, or the infection can progress to late neurosyphilis.\textsuperscript{161} The forms of involvement are meningeal, vascular, and parenchymal. Meningeal and vascular forms often occur together as meningovascular syphilis, are inflammatory in nature, and are caused by focal syphilitic endarteritis in the brain, meninges, and spinal cord leading to infarcts and transitory or permanent ischemic incidents.\textsuperscript{159} The parenchymatous form is neurodegenerative.\textsuperscript{159} Many patients with neurosyphilis are asymptomatic. Asymptomatic neurosyphilis is characterized by the presence of CSF abnormalities consistent with neurosyphilis in patients with evidence of syphilis, in the absence of neurological signs or symptoms. In the pre-penicillin era, this characterization was applicable in 20\% of patients with primary and secondary syphilis and 13.5\% of those with latent syphilis.\textsuperscript{162} With the resurgence of syphilis, neurological manifestations have changed: meningeal and vascular forms are more commonly seen, whereas parenchymatous neurosyphilis has decreased in incidence.\textsuperscript{163}

Early neurological involvement is frequent. CNS invasion occurs in 25\% to 60\% of patients with primary or secondary syphilis.\textsuperscript{161} Syphilitic meningitis may occur at any stage of the disease but is usually seen within the first 2 years.\textsuperscript{160} Symptoms are nonspecific and include fever, headache, confusion, and signs of meningeal irritation. Complications include acute hydrocephalus and cranial nerve abnormalities. The most commonly affected cranial nerves are VII and VIII, and sensorineural hearing loss occurs in up to 20\% of patients.\textsuperscript{164} Meningovascular syphilis occurs in 0.3\% to 2.4\% of all patients with syphilis,\textsuperscript{165} usually within 10 years of infection.\textsuperscript{160} The average latency of meningo-vascular neurosyphilis is 7 years.\textsuperscript{158} Stroke symptoms may be acute or subacute.\textsuperscript{166} Neurosyphilis should be considered in the differential diagnosis of any patient with stroke of undetermined etiology, especially stroke in the young.\textsuperscript{165} Unlike other stroke syndromes, neurosyphilis can present with a prodrome of headache, vertigo, insomnia, emotional lability, or personality changes, which may occur months prior to the actual infarction.

Both the anterior and posterior circulation can be affected, but the anterior circulation is more commonly involved.\textsuperscript{166} Pure brachyneminal syndromes,\textsuperscript{166} as well as persistent basilar stenosis despite adequate response to treatment,\textsuperscript{166} have been reported. Angiographically, large vessels appear with concentric narrowing, and smaller vessels have focal narrowing and dilatation.\textsuperscript{160} As opposed to atherosclerotic disease, syphilis is more likely to involve the supraclinoid portion of the internal carotid artery, and plaques in syphilitic arteritis are longer and smoother.\textsuperscript{170} Pathological features in meningo-vascular syphilis include lymphocytic infiltration of the meninges and perivascular spaces with diffuse thickening, Heubner arteritis, and Nissl arteritis. Either pathology can lead to vessel narrowing and occlusion with subsequent ischemia and infarction.\textsuperscript{171} Classic late parenchymal neurosyphilis, presenting as general paresis or tabes dorsalis, results from extensive damage to the parenchyma in the brain or spinal cord.\textsuperscript{159} Both forms have become rarer in the antibiotic era. Early symptoms of paresis mimic other forms of dementia, with
forgetfulness, irritability, personality changes, speech impairment, sleep changes, and psychotic symptoms. Late symptoms progress toward increased emotional lability, further memory impairment, disorientation, delusions, seizures, and a wide range of psychiatric manifestations. Neurological signs commonly found are dysarthria, tremors, and optical abnormalities. Small, irregular pupils that accommodate but do not react to light (Argyll Robertson pupils) are seen in 50% of patients, and 20% develop optic atrophy. Neurosyphilis mimicking herpes simplex encephalitis, with seizures and parenchymal abnormalities, has been reported in young patients. Pathologically, atrophy of the frontal and temporal lobes occurs with sparing of the motor, sensory, and occipital cortices. The cerebellum and basal ganglia may be affected. Chronic meningitis is most pronounced over the areas of atrophy. The primary pathological process in tabes dorsalis is demyelination and degeneration of the posterior column, dorsal roots, and dorsal root ganglia. The characteristic symptom of “lightning pains” in the lower extremities occurs in 75% to 90% of patients. Ataxic gait results from impairment of position sense. Furthermore, paresthesias are common. Hips, knees, and ankles can develop a trophic degenerative joint disease known as Charcot joint, and 10% to 15% of patients will experience a visceral crisis consisting of sudden epigastric pain, vomiting, and acute urinary retention.

Syphilis and HIV

By altering the normal immune responses, HIV infection may affect the presentation, diagnosis, and natural course of syphilis. The stages of syphilis are less defined in the setting of coinfection with HIV. HIV patients with syphilis are more likely to develop neurosyphilis than the general population, and the degree of immunosuppression correlates with the risk of development of neurosyphilis. The use of cART reduces the risk of developing neurosyphilis by 65%, and a CD4+ cell count less than 350 cells/mm³ increases the risk. The incidence of reinfection or relapse is also higher in HIV-infected patients. Among HIV-positive patients with untreated late syphilis, the prevalence of neurosyphilis may be as high as 23.5%. Neurological manifestations of syphilis and HIV infection overlap in many aspects: both can cause chronic meningitis, vasculitis, stroke, cranial neuropathies, cognitive decline, and myelopathy. The most common manifestations of neurosyphilis in one series were uveitis (33%), altered cognition (20%), gait abnormality (9%), hearing loss (4.2%), and Bell palsy (4.2%). Of HIV-infected patients with neurosyphilis, 60% to 70% may be asymptomatic. All patients diagnosed with syphilis should be screened for HIV infection as well, and vice versa, and neurosyphilis should be considered in any HIV-positive patient with unexplained neurological symptoms.

Diagnosis

Serological testing including nontreponemal and treponemal antigen tests is the standard detection method in the United States for all stages of syphilis. Nontreponemal tests, including the RPR and VDRL tests, are based on a nonspecific reaction with lipoidal antigens of T. pallidum or lipoidal antigens secondary to the immune response to treponema. They are used to screen and can be used to monitor response to therapy because they correlate with disease activity. False-positive results can occur in the settings of acute infectious illness, infection with other spirochetes (e.g., Lyme disease), recent immunization, multiple blood transfusions, or pregnancy, or chronically in collagen vascular diseases, hypergammaglobulinemia, or leprosy. The presence of HIV may cause a false-positive VDRL test result due to polyclonal B-cell activation with hypergammaglobulinemia. The “prozone effect,” a false-negative RPR test result in the setting of markedly elevated antibody titers interfering with the antigen–antibody interaction necessary for a positive reaction, is more likely to occur in HIV-positive patients. A false-negative VDRL test result may occur in the later stages of neurosyphilis in 25% to 40% of patients. All positive screening results should be confirmed with a treponema-specific test. Treponemal tests include syphilis IgG, fluorescent treponemal antibody absorption test (FTA-ABS), T. pallidum hemagglutination (TPHA), automated microhemagglutination (MHA-TP), and T. pallidum immobilization test. Once positive, FTA-ABS and TPHA remain positive for life. A negative serum FTA-ABS test rules out syphilis infection. False-positive treponemal test results can occur in the setting of abnormal serum globulin levels (collagen vascular diseases, autoimmune hemolytic anemia, alcoholic cirrhosis, pregnancy) and also in infection with Leptospira or Borrelia. For the diagnosis of neurosyphilis, a combination of a reactive serological test and elevated CSF protein or cell count, or a positive CSF VDRL test, is necessary. The CDC recommends a lumbar puncture for patients with neurological or ophthalmic disease, syphilis when initial treatment has failed, symptomatic tertiary syphilis, and HIV disease plus late latent syphilis or syphilis of unknown duration. CSF abnormalities usually include pleocytosis with lymphocytic predominance, elevated protein, and low glucose. Entirely normal CSF is found in up to 4% of patients with symptomatic neurosyphilis and is even more likely in advanced stages. A false-positive CSF VDRL test result is rare but can be found if the CSF is contaminated with peripheral blood. The CSF FTA-ABS test is most helpful when neurosyphilis is suspected but the CSF VDRL test is negative. The CSF FTA-ABS test can be controversial because the presence of antibodies to T. pallidum in the CSF may reflect systemic immunoglobulins that have crossed the blood–brain barrier, and distinction is possible with an elevated IgG index or oligoclonal bands. If serum FTA-ABS is reactive and CSF FTA-ABS is nonreactive, neurosyphilis is unlikely. Caution is necessary in interpreting CSF results in HIV-positive patients with syphilis because elevated total protein, lymphocytic pleocytosis, and immunoglobulins all can be attributed to HIV alone. Limited data suggest that a cutoff of 10 cells/mm³ in HIV-positive patients on cART and 20 cells/mm³ in patients not on retroviral therapy may improve the specificity for diagnosing neurosyphilis. Brain imaging does not show pathognomonic findings. Whether and which abnormalities can be found largely depends on the presentation and stage of disease. The most common findings are white matter changes.
Treatment

Treatment guidelines are based on disease staging. Later stages require longer durations of treatment. Primary, secondary, and early latent syphilis should be treated with benzathine penicillin G, 2.4 million units intramuscularly once, or alternatively with doxycycline, tetracycline, or ceftriaxone. For late syphilis, the penicillin dosing is the same but is given every week for 3 weeks. Neurosyphilis at any stage is treated with aqueous crystalline penicillin G, 3 to 4 million units intravenously every 4 hours, 18 to 24 million units per day intravenously for 10 to 14 days, or procaine penicillin 2.4 million units intramuscularly once daily plus probenecid 500 mg orally 4 times daily for 10 to 14 days. The regimen for late-stage neurosyphilis is then followed by benzathine penicillin G, 2.4 million units intramuscularly every week for up to 3 weeks. Alternative regimens include ceftriaxone 2 g intravenously or intramuscularly daily for 10 to 14 days. Oral penicillin preparations are not recommended. Treatment monitoring with CSF analysis is done every 6 months until the cell count normalizes. If the CSF does not normalize within 2 years, or the pleocytosis does not decrease by 6 months, treatment is considered to have failed. Within the first 24 hours of treatment, the Jarisch-Herxheimer reaction, an acute febrile illness with headaches, myalgia, or other constitutional symptoms, may occur and is treated supportively.

Listeria Monocytogenes

Epidemiology

Listeria monocytogenes is a gram-positive, facultative intracellular anaerobic bacterium with a notorious tropism for the CNS. Resistance to infection depends primarily on cell-mediated immunity. Outbreaks and sporadic episodes are usually foodborne. While most cases are sporadic, common source outbreaks are usually related to dairy products. As many as 1% to 5% of humans are asymptomatic intestinal carriers, and as many as 26% of people in contact with symptomatic patients are carriers. The 2 major routes of infection are via retrograde neural crossing of the oral epithelium, and hematogenous. Occasionally, the bacterium enters through a skin defect or directly through the eye. The average time from ingestion to presentation is 1 month. Listeriosis is a reportable disease for the CDC and state departments of public health. Case numbers increase over the long term in 6%. Peripheral leukocytosis may or may not be present (39% exceeding 10 000 cells/mm3). Nonspecific markers such as C-reactive protein and erythrocyte sedimentation rate are elevated in more than 90% of patients. Transaminitis is commonly found and typically exceeds 100 U/L. Typical CSF findings include a mild pleocytosis (5-100 WBC/mm3) with polymorphonuclear predominance in 67%, nearly always elevated total protein, and hypoglycorrhachia in 39%. High pleocytosis with a WBC count greater than 5 000/mm3 or total protein of more than 200 mg/dL is uncommon. The CSF gram stain is positive in 31% to 36% of patients; the CSF cultures return positive in at least 80% of patients with meningitis and meningoencephalitis, whereas blood cultures are positive only in 59% to 73%. The imaging findings in Listeria meningitis are not different from those in bacterial meningitis to be particularly affected. In 10% of patients, antineoplastic chemotherapy has been used within the preceding 6 months. Listeriosis is usually community-acquired; only 3% to 12% of cases occur among hospitalized patients.

Listeria Meningitis and Meningoencephalitis

In the majority (97%) of patients, CNS listeriosis manifests as meningitis or meningoencephalitis. Regardless of age, listeria is one of the 4 major pathogens of community-acquired meningitis, with an incidence of 0.2 per 100 000, comprising 8% of meningitis cases in the United States. After ingestion, the portal circulation carries the pathogen to the liver, where hepatic invasion occurs. Upon release of the pathogen from the liver, patients become bacteremic, with a systemic illness that can be mild or potentially fatal. Otherwise healthy patients initially often remain asymptomatic. Symptoms of gastroenteritis occur in as few as 16% of patients with CNS involvement. More than 50% of immunocompromised patients present with a febrile syndrome. After seeding into the CNS occurs, the most common findings are fever (91% to 100%, regardless of immune status), altered mental status (65%), and headache (46%). Headache is reported much less frequently than in bacterial meningitis of other origin, in which 90% of patients complain of headaches. Only 28% of patients with Listeria meningitis are found to have the classic triad of fever, headache, and altered sensorium. Focal neurological findings occur in 16% to 35% of patients, and 4% to 12% of patients experience seizures. These seizures are mostly generalized; only less than 10% are focal. The average duration of symptoms prior to admission is 3.2 days. During hospitalization, altered level of consciousness is the most common neurological finding (77% to 85%). Most focal neurological symptoms are present on admission; seizures may begin later in the course. Cranial neuropathies may occur, and cranial nerves III, VI, VII, XI, and X are most commonly affected.

The overall mortality is estimated to be 24%, higher (38%) in immunocompromised patients, and 15% in otherwise healthy patients. Mortality is also higher in patients with seizures and older patients. Of those who survive, 13% had some form of neurological deficit at discharge in one series, which persisted over the long term in 6%. Peripheral leukocytosis may or may not be present (39% exceeding 10 000 cells/mm3). Nonspecific markers such as C-reactive protein and erythrocyte sedimentation rate are elevated in more than 90% of patients. Transaminitis is commonly found and typically exceeds 100 U/L. Typical CSF findings include a mild pleocytosis (5-100 WBC/mm3) with polymorphonuclear predominance in 67%, nearly always elevated total protein, and hypoglycorrhachia in 39%. High pleocytosis with a WBC count greater than 5 000/mm3 or total protein of more than 200 mg/dL is uncommon. The CSF gram stain is positive in 31% to 36% of patients; the CSF cultures return positive in at least 80% of patients with meningitis and meningoencephalitis, whereas blood cultures are positive only in 59% to 73%. The imaging findings in Listeria meningitis are not different from those in bacterial meningitis.
of other origin. Head CT is unremarkable in 60% of patients. If the head CT is abnormal, the most common findings are focal lesions or hydrocephalus.

**Listeria Cerebritis or Abscess**

Listeria cerebritis and abscess only account for 2% to 3% of all cases. Although up to 25% of patients are healthy, the typical feature in those with cerebritis is the presence of an underlying illness with immunosuppression, often a hematological malignancy or renal transplantation or autoimmune disease, diabetes, alcohol abuse, cirrhosis, or AIDS. Men are affected 6 times more frequently than women. The most common symptoms are fever, headache, and altered sensorium, but meningeval signs are usually absent. The most common focal findings are hemiparesis or cranial nerve palsy (VI or VII). A preferred abscess location is in one of the cortical lobes, but basal ganglia seem to be preferred as well. Spinal cord abscess has been reported 6 times in the literature, with 4 of the 6 patients being otherwise healthy. As opposed to meningitis, the CSF often does not display a marked pleocytosis. Total CSF protein is elevated with a mean of 180 mg/dL, and glucose is usually normal. CSF cultures are of low yield and may be positive in 50% of patients. Blood cultures, however, are positive in more than 80% of patients and were positive in nearly all cases in one series.

**Brainstem Encephalitis (Rhombencephalitis)**

Rhombencephalitis is an uncommon but possibly underrecognized form of CNS listeriosis. The reported frequency ranges from less than 1% to 24% of listerial CNS infections. As opposed to other forms of CNS listeriosis, 72% of rhombencephalitis patients are otherwise healthy; an underlying immunosuppressed condition, mostly chronic corticosteroid treatment or alcoholism, is found in 10%, and other associated medical (but not immunocompromising) conditions are found in the remaining 18%. In this syndrome, there is a striking absence or subtlety of classic meningitis symptoms relative to brainstem symptoms. A biphasic presentation, however, is typical, with the first phase being a prodrome of headache, nausea, vomiting, fever, malaise, and vague neurological symptoms such as weakness, dizziness, and disorientation for 1 to 16 days. On presentation, the majority of patients have normal mental status, and brainstem symptoms and signs then quickly dominate the clinical picture. Unilateral lower motor neuron facial palsy is the first and most frequent sign (78%) and is usually followed by unilateral progression with descending cranial nerve signs and ipsilateral long-tract deficits. Anatomically, involvement of the pons and medulla is seen in two-thirds of patients, whereas the midbrain is affected in a minority of patients. Progression to respiratory failure due to medullary involvement or aspiration, dysphagia, or impaired consciousness occurs in 41% of patients. Differential consideration of viral encephalitis, vasculitis, or vertebral vascular disease may lead to a delay in diagnosis and antibiotic treatment. CSF lymphocytes or monocytes predominate the cell differential in 58% of patients, but 22% have no CSF pleocytosis. In 95% of patients, the cell count is less than 15 000 cells/mm³. A repeat lumbar puncture may be useful because 90% demonstrate a greater degree of pleocytosis in the second analysis. Oligoclonal bands were found in 43% of the initial CSF analyses in one series. CSF gram stain was positive in less than 4%, and CSF cultures were positive in one-third initially and 41% on the second analysis. Blood cultures are positive in 50% initially and 61% when repeated. While CT scans are normal in 57% initially, MRI is the study of choice and may demonstrate ring enhancement with T1 weighting and increased intensity with T2 weighting or T2 hyperintensity with subtle T1 hypointensity without enhancement after 48 hours of brainstem symptoms.

**Treatment of Listeria CNS Infections**

Ampicillin and penicillin are used in 57% to 83% of cases. Ampicillin is preferred because of its effectiveness against a greater number of strains of Listeria and its ability to reach therapeutic concentrations in the setting of inflamed meninges. The dosing for ampicillin is 2 g intravenously every 4 hours. Resistant organisms have not yet been of clinical relevance except for a solitary case report in 1984. Empirical treatment is recommended for patients with immunosuppression, patients aged 50 years or more, or patients with a CSF gram stain revealing gram-positive bacilli. The addition of gentamicin is often suggested, but aminoglycosides have poor penetration of the blood–brain barrier. Intraventricular administration is an important alternative because it has good CSF penetration and is bactericidal for Listeria. Given the intracellular location of the organism, a prolonged period of therapy of at least 13 to 21 days is needed. In immunocompromised patients in whom impaired clearing of infected cells may contribute to relapses, a course of 3 to 4 weeks is recommended. Surgical treatment often is required for hydrocephalus. No randomized controlled clinical trials have been done to establish whether a better treatment regimen exists for meningitis or the other CNS infections caused by Listeria. For abscess, at least 5 to 6 weeks of antibiotic treatment is required. The usual regimen consists of penicillin or ampicillin, but some success has been reported with the addition of chloramphenicol. Surgical drainage of the abscess may be required but does not seem as crucial as it is in patients with other bacterial abscesses. The treatment for rhombencephalitis also mostly consists of ampicillin. An added benefit of gentamicin remains inconclusive: in one series, 69% of patients who received combined initial therapy survived, similar to the survival rate among patients receiving ampicillin or penicillin alone. Without antibiotic therapy, Listeria rhombencephalitis is uniformly fatal.

References are available online at www.rush.edu/neurosciencereview.
Chronic Epilepsy Due to Low Grade Temporal Lobe Tumors and Due to Hippocampal Sclerosis: Do They Differ in Postsurgical Outcome?

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Introduction

Since the publication of the report by Hughlings Jackson in the 1880s,1 it has been known that seizures may sometimes be the only manifestation of a brain tumor. In large series, supratentorial tumors constituted 10% to 40% of the pathological diagnosis in patients undergoing surgery for seizure disorders.2,3 However, temporal lobe tumors, especially the low-grade neoplasms, are among the most common causes of seizures in patients referred for epilepsy surgery.4-6

The exact causes of temporal lobe tumor-induced seizures and their true incidence among epilepsy patients are unknown. It has been reported that tumor patients tend to be younger with the tumors having well-differentiated histological features, close proximity with the limbic system, and a distinctive growth pattern of low-grade nature presenting often with seizures alone.2,3,7 However, temporal lobe tumors, especially the low-grade neoplasms, are among the most common causes of seizures in patients referred for epilepsy surgery.4-6

The exact causes of temporal lobe tumor-induced seizures and their true incidence among epilepsy patients are unknown. It has been reported that tumor patients tend to be younger with the tumors having well-differentiated histological features, close proximity with the limbic system, and a distinctive growth pattern of low-grade nature presenting often with seizures alone.2,3,7

In spite of these established observations, the management strategy commonly used for patients with seizures without other signs and symptoms remains controversial regarding the decision to perform a lesionectomy or to include the epileptogenic cortex, most commonly the amygdala and hippocampus, in the excision.

The most common pathological lesion in temporal lobe epilepsy (TLE) surgery has been hippocampal sclerosis (HS) as established by the works of Falconer8 and of Margerison and Corsellis.9 The important role of the hippocampus in epileptogenesis in medically refractory TLE has been demonstrated in the recent imaging advancements such as hippocampal volumetry and T2 relaxometry.10 However, the TLE lesion may be found beyond the hippocampal formation, and tumors as well as vascular malformations could be identified by magnetic resonance imaging (MRI) in such cases.11,12 Postprocessing MRI techniques, like quantitative volumetric analysis, identified extrahippocampal abnormalities such as temporal lobe volume loss and entorhinal cortex atrophy in TLE patients, suggesting that TLE might depend on a more widespread temporal lobe disturbance or might result from dual pathology, that is, HS with abnormal neocortical structures.13,14

The significance of these dual pathologies lies in the fact that the treatment outcomes may not reach the expected goals.

It has been reported that the best TLE outcomes come from the surgical resection of the amygdala and hippocampus as well as the temporal lobe tumor.15 These excellent outcomes can be explained by the fact that the whole epileptogenic tissue has been excised as demonstrated by electrophysiological investigations. In some series, patients with HS and ganglioglioma have the best outcomes, and patients with dysembryoplastic neuroepithelial tumor may exhibit seizure relapses after surgery.16-18

The confounding factors in TLE may result in differences in outcome following surgical treatment of HS and tumors, quite unlike the reports in the literature. The demographics of the patient population studied at each center for epilepsy surgery may also influence the postsurgical outcome. With the available technology at present, the diagnostic delay has been considerably reduced for both HS and tumors. It needs to be determined whether the delay in surgical intervention and resultant postsurgical outcome are any different between these two entities that have been reported to have the best surgical results.

Materials and Methods

A retrospective analysis was performed from our Institutional Review Board-approved epilepsy surgery database. The database started with cases operated in 1997. The series ended in 2008. The additional 79 cases were nonlesional epilepsy or included other lesions (vascular, heterotopias, etc). From the data, all
surgically treated cases of chronic epilepsy due to low-grade temporal lobe tumors and cases of HS were selected. Patients with isolated HS were identified for comparative analysis. All cases were categorized only after pathological confirmation. Treatment was considered failed due to lack of efficacy of 2 or more antiepileptic drugs (AEDs) in monotherapy and 1 or more AED combinations. Important variables such as gender, age of onset of seizures, preoperative duration, age at the time of surgery, postsurgical outcome, and postsurgical follow-up duration were compared between the 2 groups. All patients were referred by epileptologists, were reviewed in a multidisciplinary epilepsy conference, and had conditions that were deemed medically intractable by consensus of a team of 7 epileptologists.

All medically refractory HS cases met Kwan and Brodie’s definition.19

As noted by Berg et al,20 HS patients seem to have a longer interval from seizure onset to becoming medically refractory. Also, the first seizure for HS patients is often not the habitual seizure type referred for surgery, and there is often a long interval from first seizure to onset of habitual temporal lobe seizures. We do not have this detail of seizure history available. On the other hand, the phenomenon of the first seizure not being the habitual seizure, and a potential long interval between first seizure and intractability, is also true in cases of low-grade glioma causing seizures. Thus we believe our proposed findings are still valid.

Postsurgical outcome was measured by Engel’s classification. In our total temporal lobe series in this period, 11 patients were lost to follow-up. These patients were excluded from analysis up front and not included in this series. All cases of HS were categorized as such only after pathological confirmation with microscopic evidence of MTS (medial temporal sclerosis).

Statistical evaluations were performed by univariate (Fisher’s test; GraphPad software, San Diego, California; t test, 2-tailed, Excel, Microsoft Office, Microsoft Corp, Redmond, Washington) and multivariate (logistic regression) analyses (SAS version 9.2, Cary, North Carolina). Statistical significance was assumed at a P value of less than .05. Both groups were compared in a combined data set for differences in the variables mentioned above.

Results

Among the 233 patients with chronic TLE, 34 patients had low-grade tumors (14.6%) and 120 patients were surgically treated for HS (51.5%). The tumor group consisted of 18 males and 17 females, and the HS group consisted of 56 males and 64 females. The tumor patients had a mean age of onset of 18.1 years, and the preoperative duration of epilepsy was 13.1 years (Table 2). Compared to the 120 HS patients, both of these factors were significantly different (P < .001). Age at the time of surgery for tumors was 31.08 years (P = .5). Tumors were left-sided in 20 patients. During the tumor removal, the amygdala was completely resected in 75% of patients. Hippocampal resection was complete in 24% and was partial in 39%, and the hippocampus was not resected in 37%. However, the outcome had no correlation with hippocampal resection (or with resection of the amygdala). Low-grade astrocytoma (N = 10; 29.4%), ganglioglioma (N = 10; 29.4%), and oligodendroglioma (N = 9; 26.5%) constituted most of the tumors. The second group consisted of patients with HS without any other coexisting pathology. Mean postsurgical follow-up was 5.1 years (SD = 3.91 years) for tumor patients and 5.21 years (SD = 3.59 years) for HS patients (no statistically significant difference).

Good postsurgical epilepsy outcome (Engel’s class I) was achieved in 88.2% of tumor patients and 71% of HS patients, whereas poor outcome (class III or IV) was seen in 5.9% and 16.7%, respectively. In multivariate logistic regression (forward stepwise) analysis of all the previously stated variables, the groups differed significantly in preoperative delay to surgery and Engel’s class outcome (Table 1).

Class 1a Outcome Analysis

There were 35.3% patients with TLT in class 1a, compared to 36.6% of patients in the HS group. This difference was not statistically significant (P = 1; Fisher’s exact test).

Surgical Management

A summary of our surgical practice is provided below.

Preoperatively, all patients underwent noninvasive video electroencephalography and neuropsychological examination. Wada testing was done selectively.2,24,26

We employed, in most dominant hemisphere cases, cortical stimulation mapping to localize speech function. All tumor resections were performed using neuronavigation. After the initial image integration and functional mapping procedure, a transcortical approach was used to gain access to the lesion and a gross-total resection was performed under the microscope.

Resection of the amygdala and hippocampus was dependent upon several factors including preoperative neuropsychological data, Wada testing, preoperative and intraoperative localization,

<table>
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<th>Variable</th>
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<th>Upper</th>
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<td>1.006</td>
<td>3.758</td>
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Table 1. Multivariate (Forward Logistic Regression) Analysis of Variables for Significant Differences Between the Two Groups (Dependent Variable Was Pathology: Hippocampal Sclerosis and Tumor)
The neuropsychological data and Wada data were used to plan resection after resection of the tumor if the ECoG findings in rare cases. Occasionally ECoG would persuade us to further data from semiology, EEG, MRI findings, and metabolic imaging. The epileptic zone was determined in our standard way, using involvement of the amygdala and hippocampus) in addition to the TLE patients and nontumor TLE patients was that in all patients, however, electrocorticography was employed, and in some cases where complete hippocampectomy was performed. In all patients who underwent a mesial temporal resection, the amygdala was resected to the level of the entorhinal sulcus. Most of the low-grade tumors could be excised completely because they rarely extended above this line. Safe excision of the tumor could be performed, sparing the anterior choroidal artery and the optic tract.

Aspiration of the hippocampus was pursued subsequently, with resection of head and body continued to the ambient cistern in cases where complete hippocampectomy was performed.

Tumor cases focused primarily on complete tumor resection; however, electrocorticography was employed, and in some cases the resection included epileptogenic, presumed nonneoplastic tissue. The decision to extend a resection was based on the total clinical picture as measured by the risks and benefits of further resection. Factors considered were proximity of speech function, neuropsychological data, Wada test data, and severity of electroencephalogram (EEG) and electrocorticography (ECoG) findings.

The only difference in the extent of resection between tumor TLE patients and nontumor TLE patients was that in all patients, we attempted a gross total resection of the tumor (often involving the amygdala and hippocampus) in addition to the epileptic zone as determined in our standard epilepsy evaluation. The epileptic zone was determined in our standard way, using data from semiology, EEG, MRI findings, and metabolic imaging in rare cases. Occasionally ECoG would persuade us to further the resection after resection of the tumor if the ECoG findings showed persistent focal discharges with a broad field of spread. The neuropsychological data and Wada data were used to determine the likelihood of persistent memory or speech deficits with a more extensive resection. Factors that led to a more extensive resection included MRI findings of mesial temporal sclerosis, nondominant temporal lobe, evidence of poor ipsilateral memory function on neuropsychological and Wada memory testing, and intraoperative ECoG findings of intraoperative seizure or persistent focal discharges with a broad field of spread. In the tumor patients, the ECoG was repeated after the tumor resection, with the resection extended if these findings were present. In all patients who underwent a mesial temporal resection, the amygdala was resected to the level of the entorhinal sulcus at an axial level drawn between M1 and the choroidal fissure. When a complete hippocampectomy was performed, it was done to the coronal plane of the quadrigeminal plate.

**Postoperative Complications**

We had no cases of homonymous hemianopia or disabling visual field defects. We did not quantify visual field loss that was less than a superior quadrant. One patient had wound infection and required bone flap removal. A second patient had transient facial nerve palsy and dysphasia. (Complications were very few, and most of them were in nonlesional TLE patients.)

This analysis suggests that there was significant delay in the surgical treatment in the HS group compared to the TLT group. The overall outcome for the HS group was also worse compared to that of the TLT group in our patient population, although class 1a had no significant difference. It may be possible that these two factors were interrelated, although we did not find any correlation in our group of HS patients. An additional group of dual pathology patients with adequate numbers for analysis might have changed the results.

**Discussion**

HS was the pathology in about 65% of patients who underwent surgery for intractable TLE (51.5% in our series). In the cohort of Tassi et al, the presence of HS was observed in 48% of the patients, and in most of these patients, it was in association with other pathologies, mainly cortical dysplasia. Several studies of TLE focus on HS as the primary lesion, giving an erroneous impression that these entities are one and the same.
Tumors and TLE

The incidence of tumors producing TLE has been reported to be between 11% and 56%, a very wide range that results from the difficulties in making a tissue diagnosis from the fragmented surgical specimen. In the series of Tassi et al., 33% of the patients had tumors as a possible cause for TLE, and the authors acknowledge a referral bias because patients with a long history of epilepsy reach their center. In our series, 14.6% of epilepsy patients showed neoplasms on histopathology. On the other hand, HS occurred in half (51%) of this epilepsy patient population.

Although HS is present with other major neuropathological findings in around 30% of TLE surgical cases, the association of HS with tumors is variable. In the series of Tassi et al., HS was coupled with a tumor in only 8% of cases. We had two cases of tumors mixed with HS, thus showing that the association is rare. Perhaps in cases of dual pathology where the tumor does not directly involve the hippocampus, there would be EEG evidence of hippocampal involvement distant from the tumor.

In two large series from the Montreal Neurological Institute, 15% to 20% of surgically treated epilepsy patients harbored mass lesions, and 74% of the tumors were gliomas. In these and other series, temporal lobe tumors were found to be the largest group among tumor-related epilepsy cases with a rate of 38% to 76%. Temporal lobe tumors are not homogeneous lesions, and postsurgical outcome can be improved, especially with seizure management, if the operative approach is based on the subgroups defined by the anatomical location of the tumor. This finding is supported by our case cohort, with nearly 90% of patients having good postsurgical seizure outcome. This outcome is much better than that of the pure HS cohort in our experience.

TLE and Temporal Lobe Tumors: A Unique Entity

TLE with temporal lobe tumors as the substrate of seizures exhibits certain distinct features. Fried et al. described temporal lobe tumors associated with intractable seizures as a distinct clinicopathological group. The patients in this group were young, and the biological behavior of the tumor was particularly indolent. Interestingly, a male predominance was observed in several series, ranging between 70% and 73%. Nearly 91% of tumors were found within or adjacent to the mesial structures, and the hippocampus with frequent involvement of mesial temporal structures. Spencer’s group identified the following characteristics of tumor and TLE: young patient age, long history of seizure disorder, seizures as the only symptom and normal neurological examination, a well-differentiated pattern of the tumor, an indolent biological nature with long-term survival, and good favorable surgical outcome.

Histopathological Substrate

As reported in earlier reports, low-grade gliomas comprise the vast majority of tumors among epilepsy patients. However, discrepancies exist in the tumor subtypes (Table 2). Our previously published experience had gangliogliomas as the most common TLT. Cataltepe et al. also found that 20.6% of the temporal lobe tumor specimens contained an additional disease entity: cortical dysplasia or neuronal heterotopias in the surrounding brain tissue. In general, the discrepancies concerning the incidence of subtypes may be related to the use of different pathological criteria for the diagnosis of these controversial tumors or to the heterogeneity of the samples obtained during excision of these tumors.

Surgical Strategy

Tumor-related epilepsy has unknown mechanisms and several theories for epileptogenesis, which include pressure and irritation of underlying brain with vascular changes and neuronal alterations including the physiology of neurotransmitters and glial scar tissue. Because a structural lesion need not be a source of epileptic activity, a causal relationship has to be established between the tumor and the seizures by a thorough preoperative evaluation with video and EEG monitoring.

Nevertheless, the optimal approach remains debated: some surgeons recommend isolated tumor resection, whereas others add resection of surrounding epileptogenic mesial structures using ECoG recordings. In a study of 30 patients, Jooma et al. had significantly better outcome in patients who underwent lesionectomy alone compared to those who had resection of the lesion as well as the focus, guided by intraoperative recordings. Khajavi et al. reported in a study of pediatric patients that seizure-free outcome correlated with the extent of tumor resection but not with additional excision of the surrounding epileptogenic zone. Cataltepe et al. reported that in gross total resections, 62% of patients were seizure free, and Kirkpatrick et al. reported incomplete resection in 71% of patients and a seizure-free outcome rate of 81%, possibly by reducing critical epileptogenic mass, thus resulting in interrupted critical seizure propagation pathways.

Another important issue is the resection of mesial temporal structures. Using depth electrodes, Mathern et al. reported that in 94% of patients with temporal lobe lesions, ictal onset as observed on EEG started or first propagated in the mesial temporal contacts. These observations indicated that mesial structures are capable of generating independent seizures. The extent of hippocampal reorganization has not been studied in patients with TLT. Morris et al. recommended hippocampal resection if additional hippocampal atrophy was evident on MRI. The incidence of dual disease varies in the literature. Drake et al. found mesial temporal sclerosis in 56% of the pediatric patients with temporal lobe tumors in their series. Fried et al. suggested that the mesial structures should be resected along with the tumor in patients with mesial temporal lesions and early seizure onset. Zaatreh et al. resected the mesial structure when tumor was involved and gauged the extent of hippocampal resection depending on exact tumor location, lesion size, preoperative neuropsychological findings, and the MRI.
appearance of the hippocampus. Currently, there are no convincing data to define a clear surgical strategy. Neither hippocampal resection nor amygdala resection had any correlation with outcome in our TLT patients, possibly because of the presence of fewer poor outcomes in the cohort. Khajavi et al suggested that only the completeness of the tumor resection can determine seizure outcome in children. Zaatreh et al reached a similar conclusion in a series including both adults and children. Thom et al concluded that reexamination of all variables is necessary to improve surgical outcome because TLE is a mixed pathological entity requiring different diagnostic and surgical approaches.

Limitations
This retrospective analysis from a database suffers from the inherent drawbacks of such methods. The selective nature of the cases cannot be controlled because of the referral bias to our university. History of seizures or habitual seizures or frequency of seizures hence may not be accurate, although the duration of seizures could be reliably elicited. The phenomenon of the first seizure not being the habitual seizure, as well as a potential long interval between first seizure and intractability, is also present in patients with low-grade gliomas causing seizures. We cannot conclude causation, a clear difference in the groups caused by the length of the interval between diagnosis and surgery. We can only state that there was a difference. Thus we believe our proposed findings are still valid. We also did not attempt to break down the modest numbers for divisional analysis looking into Class 1 subgroups and the histopathological variants. However, the low-grade nature of these tumors exhibited certain definitive features that yielded better seizure outcome after surgery and lead us to propose early diagnosis of drug-resistant epilepsy with Kwan and Brody’s definition and prompt surgical treatment. The longer duration of intractable epilepsy in the HS group may be responsible for the poorer response to surgical resection.

Perspective
Our study aimed to evaluate the surgical treatment results for TLT with seizures. We compared these results with surgical treatment of HS. As expected from the results reported in the literature, we found good surgical outcome in more than 85% of TLT patients. However, we found that the two groups differed significantly in the delay to definitive surgical treatment. This observation is important because HS has good surgical outcome and the results could become even better with more timely diagnosis and surgical treatment. Prompt referral of patients with HS for surgical treatment is recommended. Such a strategy is very practical because the diagnosis of treatment-resistant TLE secondary to HS can be established after two failed AED trials at optimal dosages. Further prospective studies may establish the benefits of early surgery in HS.

References are available online at www.rush.edu/neurosciencereview.
Detection of Angiographically Occult, Ruptured Cerebral Aneurysms

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Introduction

The pattern of hemorrhage dictates the management plan for a patient with both a nontraumatic subarachnoid hemorrhage and a normal diagnostic catheter cerebral angiogram. If the pattern of hemorrhage is diffuse (not perimesencephalic or cortical), serious potential causes include thrombosed aneurysms and vascular lesions of the cervical spine. The catheter cerebral angiogram is usually repeated in a week. Prior reports have shown that in such patients with diffuse subarachnoid hemorrhage, significant pathology that requires surgical treatment is discovered on the second study 16% (7/44) of the time.1 Until such a diagnosis is made, the unpredictable potential for rebleeding is obvious and underlies the urgency in appropriate decision making.

However, when the ruptured aneurysm fails to opacify because of temporary aneurysm dome thrombosis and another aneurysm is seen, this vigilant search for the actual source of bleeding may be derailed. The treating physician may falsely attribute the hemorrhage to the visible aneurysm, anatomically exclude it, and not pursue additional surveillance investigations while the risk of rebleeding remains unchanged.

This review highlights the importance of maintaining a high degree of discipline and vigilance when confronting the situation in which a detectable vascular pathology is not consistent with the hemorrhage pattern. Thrombosed, angiographically occult ruptured cerebral aneurysms serve as an illustrative example. Even when a neighboring aneurysm is treated, if the clinical suspicion remains, repeat catheter angiography improves the odds of detecting a potentially thrombosed aneurysm that more reliably explains the hemorrhage pattern. We present two cases that demonstrate the value of appreciating the interpretation of the noncontrast head computed tomography (CT) scan and the importance of maintaining a strong clinical suspicion despite a catheter angiogram demonstrating a likely unruptured aneurysm.

Case 1

A 60-year-old woman was admitted with a headache and found to have diffuse subarachnoid hemorrhage in the right Sylvian fissure, right basal cistern, and prepontine cistern (Figure 1A). CT angiography was reported to be negative for cerebral aneurysms. Catheter angiography demonstrated a 4-mm inferiorly directed right paraclinoid aneurysm. No vascular pathology was noted in the territory of the middle cerebral artery (MCA) bifurcation on the right (Figure 1B). We proceeded with coil embolization of this putative source of the subarachnoid hemorrhage. The remainder of the patient’s hospital course was uneventful, and she was discharged home in 14 days with a normal neurological examination.

Two weeks later (4 weeks after her initial subarachnoid hemorrhage), she reported worsening headaches and was admitted to a local hospital, where a CT scan demonstrated an acute hyperdensity in the right Sylvian fissure (Figure 1C). Repeat catheter angiography demonstrated a small, previously occult 2-mm superiorly and posteriorly directed right MCA bifurcation aneurysm with a 1-mm neck. The initial hemorrhage pattern from 1 month earlier was then reevaluated, and it was decided that this aneurysm was the original one that had ruptured but was thrombosed and therefore had been angiographically occult (Figure 1D). During embolization, the neck of the aneurysm was noted to be quite narrow, barely accommodating the orifice of the 1.7F microcatheter. This newly discovered aneurysm was successfully embolized, and the patient was discharged home after several days of monitoring with a normal neurological examination (Figure 1E).

Case 2

A 47-year-old woman was admitted for a sudden-onset severe headache that occurred while she was lifting weights at the gym. A CT scan demonstrated diffuse subarachnoid hemorrhage...
involving the ambient and quadrigeminal cisterns on the left, the left Sylvian fissure, and the interhemispheric fissure. Intraventricular hemorrhage was also present (Figure 2A). CT angiography demonstrated a 2.5-mm right (contralateral) anterior choroidal artery aneurysm. Catheter angiography was performed, and in addition to the right carotid lesion, a 2-mm left posterior communicating artery infundibulum/blister aneurysm was found. Vessels near the quadrigeminal plate cistern were also evaluated and found to be normal. Catheter cerebral angiogram at 2 months shows a new aneurysm measuring 2 mm in maximal dimensions at the P2/P3 junction of the parietal occipital branch and the calcarine branch. D, Catheter cerebral angiogram after coil embolization of the left posterior cerebral artery bifurcation aneurysm.

Figure 2. A, Noncontrast head CT scan demonstrating diffuse subarachnoid hemorrhage involving the ambient and quadrigeminal cisterns on the left, the left Sylvian fissure, the interhemispheric fissure, and the intraventricular extension. B, Catheter cerebral angiogram demonstrating that in addition to the right carotid lesion, a 2-mm left posterior communicating artery infundibulum/blister aneurysm was found. Vessels near the quadrigeminal plate cistern were also evaluated and found to be normal. C, Catheter cerebral angiogram at 2 months shows a new aneurysm measuring 2 mm in maximal dimensions at the P2/P3 junction of the parietal occipital branch and the calcarine branch. D, Catheter cerebral angiogram after coil embolization of the left posterior cerebral artery bifurcation aneurysm.

In 2 months, the patient was readmitted for elective catheter angiography and had been prepared for flow diversion embolization of the left posterior communicating artery blister when a new aneurysm was found measuring 2-mm in maximal dimensions with a 1-mm neck at the P2/P3 junction of the parietal occipital branch and the calcarine branch (Figure 2C). The initial hemorrhage pattern from 2 months earlier was then reevaluated, and it was decided that this aneurysm was likely the original one that had ruptured but was thrombosed and therefore angiographically occult. During embolization, the neck of the aneurysm was noted to be quite narrow, barely accommodating the orifice of the 1.7F microcatheter. This newly discovered aneurysm was embolized, and the patient was discharged home after several days of monitoring with a normal neurological examination (Figure 2D).
Discussion

The pattern of subarachnoid hemorrhage, usually one of three types, determines the yield of finding critical lesions on subsequent studies after an initially normal cerebral angiogram. Repeat catheter angiography allows for evaluation of thrombosed aneurysms and arteriovenous malformations or fistulas. Magnetic resonance imaging (MRI) of the brain with contrast can detect neoplasms, cavernous malformations, and pregnancy-related hypertension. MRI of the cervical spine can evaluate for neoplasms, vascular malformations, and cavernous malformations. Laboratory evaluation is useful for vasculitis, coagulopathies, and drug use.

The most concerning of these lesions is that of a ruptured aneurysm. Spontaneous thrombosis of previously ruptured aneurysms has been reported dating back to the work of Dandy in 1944, in which autopsy studies suggested a 15% occurrence rate. Partial spontaneous thrombosis is more frequently seen with giant aneurysms and has been reported to occur in more than half of these cases.

Anatomic vascular mechanisms have been proposed to explain spontaneous thrombosis. Animal modeling has determined a chamber volume to orifice ratio of greater than 28:1 to be associated with spontaneous aneurysm thrombosis. Aneurysms with a small orifice experience lower flow velocity, different flow direction, and smaller shear forces than those with a large orifice.

More recent studies elaborate on these vascular anatomic mechanisms and help to explain the occurrence in smaller aneurysms as well. The authors of one study looked at 7 ruptured aneurysms that were initially angiographically occult but subsequently recanalized and found a trend of smaller aneurysms. There was no mention of neck size. All but 1 of these cases demonstrated, as in our cases, an aneurysm less than 3 mm in maximal diameter. The authors hypothesized mechanisms for the initially negative angiographic study to be related to vasospasm, thrombosis, arterial dissection, and operator interpretative error. Interestingly, the anterior communicating artery complex has been reported to be the most common site for initially occult aneurysms. The concept of the chamber volume to orifice ratio could still be involved with these smaller aneurysms because of the small orifice diameter.

Several physiologic mechanisms are thought to contribute to spontaneous thrombosis of a ruptured cerebral aneurysm. These mechanisms include increased intracranial pressure, nearby vasospasm, systemic hypotension, and possibly systemic administration of antifibrinolytics. The final common mechanism from these processes consists of lower flow within the dome of the aneurysm, which increases the propensity for coagulation. The exact role of each of these factors has yet to be clarified. One study of 83 angiographically negative subarachnoid hemorrhage patients demonstrated about an equal 5% to 6% risk of ischemic stroke regardless of whether aminocaproic acid was administered.

It is likely that a combination of vascular anatomic and physiologic mechanisms lead to spontaneous thrombosis of a ruptured cerebral aneurysm. Fodstad and Liliequist found spontaneous disappearance of ruptured aneurysms on repeat catheter angiography in 3% of patients with subarachnoid hemorrhage. Other reports, like ours, have shown subsequent recanalization after temporary thrombosis of a single aneurysm. Unfortunately, it has been reported that spontaneous intra-aneurysmal clot does not seem to protect against aneurysm rupture. Whittle et al, reporting on a series of 12 patients with partial or complete thrombosis of giant intracranial aneurysms, demonstrated that nearly half developed recurrent subarachnoid hemorrhage. The mechanism likely entails recanalization of the aneurysmal clot at some point and re-exposure of the aneurysmal wall to pulsatile arterial blood flow along with protease activity.

In our series, there were no signs of vasospasm, systemic hypotension, administration of aminocaproic acid, or a large aneurysm dome diameter. In fact, the only contributing anatomic or physiologic factors may have been increased intracranial pressure and an aneurysm neck diameter of 1 mm or less, making for a relatively large chamber volume to orifice ratio.

The successful detection of ruptured cerebral aneurysms therefore relies not exclusively on the results of the catheter angiographic images, but on thoughtful interpretation of all data available, including the clinical history and pattern of subarachnoid hemorrhage on CT. Despite being commonly referred to as the "gold standard" in cerebrovascular imaging, and despite the availability of newer applications such as 3-dimensional rotational reconstructions, there still remains a conspicuous false negative rate.

Nevertheless, both initial head CT scans were neither perimesencephalic nor cortical, and should have raised a stronger clinical suspicion for a right MCA bifurcation aneurysm in the first case, and a perhaps the unusual P2-P3 junction aneurysm in the second case. Additional investigations were indicated. The presence of multiple aneurysms in both cases served as distractions and led to premature circumvention of a rational search for the etiology of the hemorrhage.

Several published series report an incidence of multiple cerebral aneurysms of about 30%. When multiple aneurysms are present, particularly when open surgery is being considered, there is particular urgency in accurately identifying the ruptured aneurysm. Angiographic signs thought to be fairly indicative of recent rupture when multiple aneurysms are present include focal spasm, focal mass effect, and aneurysm nipples. Larger size has been traditionally reported as an important determinant of the site of rupture, but more recent series seem to suggest morphology is more significant. However, it is obvious that when the aneurysm is completely thrombosed, angiographic criteria are meaningless, and determining the cause of the subarachnoid hemorrhage in the initial stages should again depend on the noncontrast CT scan.
Exploratory surgery should be considered when there is a high clinical suspicion that a ruptured and thrombosed aneurysm exists despite a negative catheter angiographic study. Although published nearly 20 years ago, one series of 5 patients over 5 years with previous negative angiograms had aneurysms that were discovered only at surgery and were successfully clipped.10 Similarly, these patients also shared the characteristic bleed pattern highly suggestive of a ruptured aneurysm, including blood in the interhemispheric fissure for anterior communicating artery aneurysms.

**Conclusion**

Ruptured and thrombosed aneurysms pose a risk for rebleeding that may go undetected because they are angiographically occult. The presence of multiple cerebral aneurysms may further complicate efforts in accurately identifying the ruptured aneurysm because their treatment may circumvent further necessary investigations. Careful analysis of the pattern of initial bleeding on noncontrast head CT scan is valuable in successfully determining the site of hemorrhage. Despite negative angiographic studies, and even when multiple cerebral aneurysms are present, diffuse subarachnoid hemorrhage may warrant exploratory surgery or early repeat catheter angiography.

References are available online at www.rush.edu/neurosciencereview.
Minimally Invasive Thoracic Microendoscopic Diskectomy: Surgical Technique and Case Series

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Introduction

Thoracic disk herniations have been treated with a variety of surgical approaches.1 Direct posterior approaches to treat disk herniation are commonly used in the lumbar spine because retraction of the thecal sac below the conus is generally tolerated. However, the thoracic spinal cord is highly susceptible to injury with even minimal retraction, and efforts to perform thoracic diskectomy through a direct posterior approach have frequently resulted in poor outcomes.1 Posterolateral approaches, including costotransversectomy and transpedicular approaches, require removal of supporting bone structure from the vertebral column; although these approaches are substantially safer than direct posterior approaches, the amount of bone that must be removed may be a cause of significant postoperative pain and morbidity. Lateral and anterior approaches allow direct access to the disk with reduced risk to the spinal cord; however, these approaches are associated with increased risk to the vital structures of the thoracic cavity. In addition, transthoracic approaches have significant morbidity secondary to pain, difficult ventilation, shoulder girdle dysfunction, and wound healing problems.2,5 Additional complications of anterior approaches include pleural effusion, pulmonary contusion, hemothorax, and chylothorax.2,6,7

In an effort to decrease the morbidity associated with conventional open procedures, recent advances in minimal access technologies have led to the application of minimally invasive approaches to the treatment of thoracic disk herniation. Until recently, the vast majority of these advances were based on thorascoscopic techniques. Thorascopy and later video-assisted thoracoscopic surgery (VATS) were developed to address pathology of the thoracic cavity and subsequently adapted for thoracic spine surgery in the early 1990s.3 Reports have documented the capacity of VATS to provide the same exposure as the transthoracic approach and to enable thoracic diskectomy.9,10 However, VATS for the treatment of thoracic spine disease has several limitations, including the attendant risks of entering the chest and a steep learning curve, which have limited its widespread use.8,11 These limitations have motivated the development of minimally invasive posterior approaches to address thoracic disk herniation, including endoscopic lateral extracavitary,12 transpedicular,13 and thoracic microendoscopic diskectomy (TMED).14,15

The TMED approach is a modification of the lumbar microendoscopic technique that has been used with great success in the treatment of numerous pathologies of the lumbar spine, including stenosis,16 disk herniation,17 and instability.18,19 TMED avoids rib resection that is required in the endoscopic lateral extracavitary approach and, in contrast to the transpedicular approach, spares most of the pedicle. Our group has previously demonstrated the cadaveric and clinical feasibility of this approach.14,15 In this article, we describe the TMED procedure and present the operative details and clinical follow-up of a series of patients with thoracic disk herniation treated with this minimally invasive technique.

Methods

Patients

Between April 2003 and June 2007, 16 patients (9 women and 7 men) underwent TMED (Table 1). Patients ranged in age from 18 to 79 years (mean, 46 years). Presenting symptoms and deficits included radiculopathy in 13 patients (81%), segmental pain in 8 patients (50%), and myelopathy in 9 patients (56%) (Table 2). Symptoms were present before surgery for a mean of 12 months (range, 3-37 months). Herniated thoracic disks were identified at the following levels: T3-4 (1 patient), T5-6 (2 patients), T6-7 (4 patients), T7-8 (3 patients), T8-9 (4 patients), T9-10 (2 patients), T10-11 (1 patient), and T11-12 (1 patient). Two
patients each had 2 separate levels of herniation, one with herniations at T5-6 and T6-7 and one with herniations at T3-4 and T9-10 (Table 1). Most patients received a trial of nonoperative treatment, including modalities such as physical therapy and steroid injections, before undergoing surgical treatment. Patients selected for surgical treatment had an inadequate response to nonsurgical therapy. A trial of nonoperative therapy before surgery was not pursued in patients with significant or progressive myelopathy. All patients underwent preoperative magnetic resonance imaging (Figures 1 and 2) or computed tomography myelography (or both) and plain radiographic imaging of the thoracic spine. One patient with a thoracic disk herniation in a purely ventral location and with evidence of significant calcification, who had previously undergone an open attempt at resection at an outside institution, was not surgically treated using the TMED procedure because it is the authors’ current opinion that such herniations are better treated with an open anterior or posterolateral approach. Clinical and operative data were collected from clinic and hospital records, and follow-up data were collected through telephone interviews with individual patients. This study was approved by the institutional review board of the University of Chicago.

### Surgical Technique

The surgical technique for TMED is a modification of the microendoscopic technique that is used successfully in the lumbar spine. The procedure is conducted using general anesthesia with the patient positioned prone on a radiolucent Wilson frame or chest rolls on a Jackson table. The Jackson table is preferred in this case to facilitate use of C-arm fluoroscopy when necessary. The patient’s arms are positioned above the patient with care to avoid extension beyond 90°. Continuous somatosensory evoked potential monitoring is utilized during the procedure, and the endoscopic and fluoroscopic monitors are positioned opposite the surgeon to facilitate visualization. Localization of the appropriate operative spinal level is of critical importance; to ensure accuracy, the authors use lateral and anterior-posterior fluoroscopy to count the spinal level from either the occiput or the sacrum. This count is done a minimum of two times in each plane and is done with live fluoroscopy for definitive confirmation of the proper level.

Once the appropriate spinal level has been identified, a superficial skin incision is made 3 to 4 cm lateral to the midline. In larger patients, a more lateral approach may be prudent to reduce manipulation of the spinal cord during disk removal. A Kirschner wire is introduced at the superior aspect of the caudal transverse process at the spinal level of interest, and a series of

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age, y</th>
<th>Sex</th>
<th>Level(s)</th>
<th>Operative Time, min</th>
<th>Blood Loss, mL</th>
<th>Hospital Stay, h</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>57</td>
<td>F</td>
<td>T6-7</td>
<td>163</td>
<td>25</td>
<td>4</td>
<td>none</td>
</tr>
<tr>
<td>2</td>
<td>34</td>
<td>M</td>
<td>T8-9</td>
<td>146</td>
<td>10</td>
<td>21</td>
<td>none</td>
</tr>
<tr>
<td>3</td>
<td>40</td>
<td>F</td>
<td>T6-7</td>
<td>221</td>
<td>100</td>
<td>4</td>
<td>none</td>
</tr>
<tr>
<td>4</td>
<td>52</td>
<td>M</td>
<td>T7-8</td>
<td>117</td>
<td>25</td>
<td>21</td>
<td>none</td>
</tr>
<tr>
<td>5</td>
<td>79</td>
<td>F</td>
<td>T5-6, T6-7</td>
<td>204</td>
<td>100</td>
<td>21</td>
<td>none</td>
</tr>
<tr>
<td>6</td>
<td>44</td>
<td>M</td>
<td>T8-9</td>
<td>80</td>
<td>20</td>
<td>4</td>
<td>none</td>
</tr>
<tr>
<td>7</td>
<td>59</td>
<td>F</td>
<td>T5-6</td>
<td>207</td>
<td>600</td>
<td>13</td>
<td>none</td>
</tr>
<tr>
<td>8</td>
<td>53</td>
<td>M</td>
<td>T11-12</td>
<td>205</td>
<td>20</td>
<td>4</td>
<td>none</td>
</tr>
<tr>
<td>9</td>
<td>36</td>
<td>F</td>
<td>T10-11</td>
<td>141</td>
<td>100</td>
<td>70</td>
<td>none</td>
</tr>
<tr>
<td>10</td>
<td>46</td>
<td>F</td>
<td>T7-8</td>
<td>123</td>
<td>10</td>
<td>4</td>
<td>none</td>
</tr>
<tr>
<td>11</td>
<td>43</td>
<td>M</td>
<td>T3-4, T9-10</td>
<td>284</td>
<td>50</td>
<td>4</td>
<td>none</td>
</tr>
<tr>
<td>12</td>
<td>49</td>
<td>F</td>
<td>T8-9</td>
<td>252</td>
<td>100</td>
<td>73</td>
<td>none</td>
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<tr>
<td>13</td>
<td>47</td>
<td>F</td>
<td>T8-9</td>
<td>127</td>
<td>20</td>
<td>4</td>
<td>none</td>
</tr>
<tr>
<td>14</td>
<td>33</td>
<td>M</td>
<td>T6-7</td>
<td>100</td>
<td>10</td>
<td>43</td>
<td>none</td>
</tr>
<tr>
<td>15</td>
<td>51</td>
<td>F</td>
<td>T9-10</td>
<td>145</td>
<td>25</td>
<td>23</td>
<td>none</td>
</tr>
<tr>
<td>16</td>
<td>18</td>
<td>M</td>
<td>T7-8</td>
<td>233</td>
<td>20</td>
<td>NA*</td>
<td>none</td>
</tr>
</tbody>
</table>

Abbreviation: NA, not available.

*Length of hospital stay not available from medical records available for review.

Table 1. Summary of Demographic Characteristics and Operative Parameters in 16 Patients Who Underwent Thoracic Microendoscopic Diskectomy

![Figure 1](image1.png) Sagittal T2-weighted magnetic resonance imaging of a patient with T6-7 disk herniation (patient 1 from Table 1).

![Figure 2](image2.png) Axial T2-weighted magnetic resonance imaging of a patient with T6-7 disk herniation (patient 1 from Table 1).
With the endoscope suitably placed, the muscle and soft tissue overlying the field are extracted with an insulated monopolar electrocautery. This exposure yields the proximal transverse process and lateral facet; as before, the proper placement of the dilator in the mediolateral axis based on patient body habitus is essential in minimizing manipulation of the spinal cord. Using a long, tapered high-speed drill, the surgeon removes the rostral aspect of the inferior transverse process and lateral facet. This maneuver reveals the pedicle of the caudal vertebral body, which is followed ventrally to the level of the disk space. At this point, the superior aspect of this pedicle may be removed with the drill to facilitate entry into the disk space.

Once the disk space has been exposed, the annulus is incised with an annulotomy knife. The herniated disk fragment is removed with a combination of curettes and pituitary rongeurs. The oblique lateromedial trajectory of the retractor, in combination with the 30° angle of the endoscope, allows for direct access to the intervertebral disk space without manipulation of the spinal cord or other neural elements. Using this technique, the surgeon can remove lateral disk herniations under direct visualization. Medial disk herniations require the use of a down-going curette or Woodson elevator to direct the fragment into the disk space, allowing it to be safely removed from the lateral annulotomy without manipulation of the spinal cord.

Once the herniated portion of the disk has been removed, the operative field is copiously irrigated, and thorough hemostasis is achieved. The retractor is removed, and the thoracodorsal fascia is closed with a absorbable suture. Interrupted subcutaneous sutures are placed, and the skin is closed with adhesive glue.

**Assessment of Outcome**

Assessment of baseline symptoms and deficits was based on review of preoperative clinic and hospital records. Postoperative outcomes of symptoms and deficits were based on telephone interviews of individual patients. Clinical outcomes were graded using modified MacNab criteria. A grade of excellent was given to patients who were free of pain and deficit, had no restriction of mobility, and were able to return to normal work and activities. A grade of good was given to patients with near-complete resolution of presenting symptoms and deficits, with residual symptoms or deficits not impeding the ability to return to at least modified work. A grade of fair was given to patients with some improved functional capacity but who remained handicapped and/or unemployed. A grade of poor was given to patients without demonstrated improvement or with worsening of presenting symptoms regardless of length of follow-up.

**Results**

A total of 18 thoracic disk herniations in 16 patients were surgically treated with the TMED technique (Table 1). No patients required conversion to an open procedure, and no patient required a blood transfusion. Only two patients (patients 4 and 12) required a partial pediculectomy (< 20%) in order to obtain adequate exposure of the disk space. The remaining diskectomies were performed through facetectomy only. Operative time ranged from 88 to 252 minutes per level (mean, 153 minutes per level). Mean operative time was not significantly different for the first 8 patients (187 minutes) compared with the last 8 patients (158 minutes; \( P = 0.3 \)), suggesting that variations in operative time were more likely attributable to patient-specific issues such as complexity of localization (eg, transitional lumbosacral vertebra or midthoracic herniation) or variation in disk consistency (eg, calcified versus soft), rather than attributable to a technical learning curve. Estimated blood loss ranged from 10 to 600 mL per level (mean, 69 mL per level). Postoperative hospital stay ranged from 4 to 73 hours (mean, 21 hours). No operative or perioperative complications were encountered. Figure 4 demonstrates the limited amount of bone removal required for the TMED procedure.
The patient's symptoms progressed, and ultimately a diagnosis of multiple systems atrophy was made. The patient had a history of multiple sclerosis. Given evidence of a herniated thoracic disk, thoracic microendoscopic diskectomy was performed to assess whether the herniated disk was contributing to myelopathy.

### Abbreviations
- LLE, left lower extremity; RLE, right lower extremity.

### Table 2. Preoperative Symptoms and Outcome Assessment in 16 Patients Who Underwent Thoracic Microendoscopic Diskectomy

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Preoperative Symptoms/Deficits</th>
<th>Follow-up Symptoms/Deficits</th>
<th>Modified MacNab Grade</th>
<th>Follow-up, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Myelopathy (moderate gait imbalance, intermittent urinary incontinence, moderate lower extremity paresthesias, left patellar hyperreflexia [3+/4]); normal motor strength; normal muscle tone</td>
<td>Unchanged from preoperative symptoms and deficits</td>
<td>Poor*</td>
<td>53</td>
</tr>
<tr>
<td>2</td>
<td>Moderate radiculopathy only; neurologically intact</td>
<td>None (resolution of radiculopathy); remains neurologically intact</td>
<td>Excellent</td>
<td>51</td>
</tr>
<tr>
<td>3</td>
<td>Severe radiculopathy; severe segmental pain; neurologically intact</td>
<td>Mild to moderate residual radiculopathy; mild segmental pain; remains neurologically intact</td>
<td>Fair</td>
<td>51</td>
</tr>
<tr>
<td>4</td>
<td>Moderate radiculopathy; severe segmental pain; neurologically intact</td>
<td>Occasional mild segmental discomfort with exertion; resolution of radiculopathy; remains neurologically intact</td>
<td>Good</td>
<td>42</td>
</tr>
<tr>
<td>5</td>
<td>Severe radiculopathy only; neurologically intact</td>
<td>None (resolution of radiculopathy); remains neurologically intact</td>
<td>Excellent</td>
<td>36</td>
</tr>
<tr>
<td>6</td>
<td>Severe radiculopathy only; neurologically intact</td>
<td>None (resolution of radiculopathy); remains neurologically intact</td>
<td>Excellent</td>
<td>35</td>
</tr>
<tr>
<td>7</td>
<td>Myelopathy (moderate gait imbalance, hyperreflexia in lower extremities [3+/4]; moderate urinary retention; normal motor strength; normal muscle tone</td>
<td>Progression of gait imbalance (moderate to severe); hyperreflexia and urinary retention remain unchanged; normal motor strength; normal muscle tone</td>
<td>Poor*</td>
<td>29</td>
</tr>
<tr>
<td>8</td>
<td>Radiculopathy; myelopathy (moderate bilateral foot numbness, erectile dysfunction, bilateral patellar [4+/4] and ankle [3+/4] hyperreflexia); normal motor strength; normal muscle tone; normal bowel/bladder function</td>
<td>Radiculopathy resolved; minimal left foot numbness; numbness otherwise resolved; erectile function not documented; normoreflexic; normal motor strength; normal muscle tone; normal bowel/bladder function</td>
<td>Excellent</td>
<td>22</td>
</tr>
<tr>
<td>9</td>
<td>Radiculopathy, segmental pain, myelopathy (LLE paresis [4-/5] and dyscoordination); normal motor strength (except for LLE); normal muscle tone; normal bowel/bladder function</td>
<td>Resolution of radiculopathy; intermittent mild residual segmental pain; resolution of LLE paresis and dyscoordination; normal muscle tone; normal bowel/bladder function</td>
<td>Good</td>
<td>21</td>
</tr>
<tr>
<td>10</td>
<td>Severe radiculopathy; moderate segmental pain; neurologically intact</td>
<td>None (resolution of radiculopathy and segmental pain); remains neurologically intact</td>
<td>Excellent</td>
<td>12</td>
</tr>
<tr>
<td>11</td>
<td>Severe radiculopathy; moderate segmental pain, myelopathy (mild gait imbalance, erectile dysfunction, mild urinary retention); normal motor strength; normal muscle tone; normal bowel/bladder function</td>
<td>None (resolution of radiculopathy, segmental pain, gait imbalance, and urinary retention); erectile function not documented; normal motor strength; normal muscle tone; normal bowel/bladder function</td>
<td>Excellent</td>
<td>10</td>
</tr>
<tr>
<td>12</td>
<td>Severe radiculopathy; myelopathy (moderate diffuse bilateral lower extremity paresthesias); normal gait; normal motor strength; normal muscle tone; normal bowel/bladder function</td>
<td>None (resolution of radiculopathy and lower extremity paresthesias); normal gait; normal motor strength; normal muscle tone; normal bowel/bladder function</td>
<td>Excellent</td>
<td>10</td>
</tr>
<tr>
<td>13</td>
<td>Moderate radiculopathy; moderate segmental pain; myelopathy (moderate gait imbalance, moderate RLE paraparesis and paresthesias; bilateral lower extremity hyperreflexia [3+/4]); otherwise normal motor strength; normal muscle tone; normal bowel/bladder function</td>
<td>Resolution of radiculopathy and segmental pain; gait imbalance resolved; remains with mild RLE paresis; RLE paresthesias resolved; normoreflexic; otherwise normal motor strength; normal muscle tone; normal bowel/bladder function</td>
<td>Good</td>
<td>9</td>
</tr>
<tr>
<td>14</td>
<td>Moderate radiculopathy, severe segmental pain, myelopathy (mild urinary retention); normal motor strength; normal muscle tone; normal bowel/bladder function; normoreflexic</td>
<td>Resolution of radiculopathy; occasional mild interscapular pain; resolution of urinary retention; normal motor strength; normal muscle tone; normal bowel/bladder function; normoreflexic</td>
<td>Good</td>
<td>4</td>
</tr>
<tr>
<td>15</td>
<td>Moderate radiculopathy, myelopathy (mild urinary retention, mild to moderate bilateral thigh and calf paresthesias, numbness in left 2nd to 4th toes); normal motor strength; normal muscle tone; normal bowel/bladder function; normoreflexic</td>
<td>Resolution of radiculopathy, urinary retention, and thigh and calf paresthesias; mild residual toe numbness; normal motor strength; normal muscle tone; normal bowel/bladder function; normoreflexic</td>
<td>Good</td>
<td>2</td>
</tr>
<tr>
<td>16</td>
<td>Mild to moderate segmental pain, myelopathy (moderate to severe gait imbalance, mild RLE paraparesis [4+/5]); otherwise normal motor strength; normal muscle tone; normal bowel/bladder function; normoreflexic</td>
<td>Resolution of segmental pain; mild gait imbalance; normal motor strength; normal muscle tone; normal bowel/bladder function; normoreflexic</td>
<td>Good</td>
<td>2</td>
</tr>
</tbody>
</table>

*The patient had a history of multiple sclerosis. Given evidence of a herniated thoracic disk, thoracic microendoscopic diskectomy was performed to assess whether the herniated disk was contributing to myelopathy.

*The patient's symptoms progressed, and ultimately a diagnosis of multiple systems atrophy was made.
Mean postoperative follow-up was 24 months (range, 2 to 53 months) (Table 2). At last follow-up, the clinical outcome of 13 patients (81%) was graded either excellent or good. One patient had residual segmental pain and radiculopathy that, although it had significantly improved from preoperative levels, warranted a grade of fair (patient 3). The 2 patients with poor clinical outcome each had another contributing diagnosis. One of these patients (patient 1) had a diagnosis of multiple sclerosis, but given the development of significant myelopathy and the discovery of a substantial thoracic disk herniation, the patient wished to pursue diskectomy in the event that the herniation was contributing to her deficits. The second patient (patient 7) presented with gait imbalance and urinary retention that continued to progress after surgery. She has since received a diagnosis of multiple systems atrophy, and her clinical findings have been attributed to this diagnosis. As of last follow-up, none of the patients in this series has developed a symptomatic recurrent herniation, and none has demonstrated evidence of segmental pain or mechanical instability attributable to the TMED procedure. None of the patients underwent any additional thoracic surgeries during the follow-up period.

Discussion

TMED is a safe and effective surgical approach for treatment of thoracic disk herniations. This procedure grants surgical access via a minimally invasive, muscle-splitting posterolateral approach that avoids entering the thoracic cavity and avoids the need for thoracic fusion. TMED offers exposure and visualization comparable to that of similar open techniques, such as costotransversectomy and the transpedicular approach, while minimizing the morbidity resulting from their associated muscle dissection. In this article, we have described the TMED procedure and documented the operative details and clinical follow-up of a series of patients treated with this minimally invasive procedure.

Overall, the results of the present study compare favorably with literature reports of patients treated with thoracotomy, VATS, costotransversectomy, endoscopic transpedicular, and lateral extracavitary approaches. However, detailed comparisons with other literature reports are limited because the patients are not matched and many variables influence the surgical outcomes among patients with herniated thoracic disks.

A recent report describes the outcomes of 7 patients with thoracic disk herniations treated surgically with a mini-open transpedicular approach. This approach requires partial or complete removal of the pedicle and a 3- to 5-cm incision. This approach contrasts with the TMED procedure, which required only partial removal of the pedicle in a small subset of cases and a 2- to 3-cm incision. Whether complete removal of the pedicle, as may be necessary with the mini-open transpedicular approach, has long-term consequences remains to be addressed.

The estimated blood loss of 600 mL in patient 7 is an outlier for this series. The medical and operative records for this patient were carefully reviewed but did not reveal a reason for this greater blood loss. This estimated blood loss may simply reflect variations in venous anatomy and venous pressures. This patient is one of the 2 patients with a poor outcome as defined by MacNab criteria. There were no documented periods of intraoperative hypotension related to the increased blood loss, and immediately following surgery, the patient’s symptoms and findings remained unchanged. However, her follow-up course was notable for gradual but progressive worsening of gait imbalance, and ultimately a diagnosis of multiple systems atrophy was made.

With regard to the short hospitalization times, even for those with myelopathy, part of the preoperative planning for our patients includes discussion of the post-operative disposition plans. In our experience, this information not only is greatly appreciated by patients and caregivers but also significantly facilitates efficient discharge.

Approximately 80% of patients in the present series had an excellent or good outcome according to the modified MacNab criteria used in this study. Only 1 patient had a fair outcome, although the patient still had significant improvement of symptoms. It is very unlikely that the 2 patients with poor outcomes would have had any better results with a different surgical approach because in retrospect the symptoms and deficits of each patient were attributable to other diagnoses. Of our patients, 13% had symptoms that were ultimately attributed to primary neurological disorders, which is a reflection of the often nonspecific symptoms and findings associated with thoracic disk herniation.

In the present series, we did not encounter any complications; this is likely due at least in part to the significant experience with minimally invasive surgery of the senior author (R.G.F.). The lack of complications does not reflect a bias in selection of more straightforward cases, such as cases with smaller, lateralized, or noncalcified herniations, because this series is consecutive except for a single, explicitly noted case. However, as with any surgical intervention, the potential for complications exists. Most of the complications that may be encountered with the TMED procedure are shared among all of the common thoracic disk excision approaches. Examples of these risks include traumatic spinal cord injury through excessive cord manipulation, spinal cord vascular ischemia secondary to hypotensive episodes, operating at the wrong level because of improper localization, and durotomy. With regard to the TMED procedure, it is important that the surgeon have adequate experience operating with an endoscope before attempting excision of a thoracic disk. The surgeon must adapt to the use of longer instruments, which provide less tactile feedback, and be comfortable operating using a 2-dimensional endoscopic monitor, which, despite providing exceptional visualization, lacks the depth of field offered by most surgical microscopes.

It is not uncommon for herniated thoracic disks to be calcified, either partially or substantially, and preoperative computed tomography may be performed in order to assess the degree of calcification. Safely excising significantly calcified thoracic disk herniations that are in a directly ventral location is particularly...
challenging using a posterior approach, especially if the herniation is enveloped by the spinal cord. In addition, calcified disks may be firmly adherent to the dura, which may increase the risk of durotomy and cord injury when excision is attempted from a posterior approach. In the present series, we excluded one patient with a significantly calcified ventral midline herniation. Instead, the patient was treated with an open posterolateral approach.25

The present study has some limitations. First, this retrospective review relied on existing medical records for the collection of clinical and operative data. However, we did confirm clinical data, including preoperative symptoms, with individual patients during follow-up telephone interviews. Second, because there was no control group, we relied on historical cohorts for comparison. Third, standardized measures of outcome were not used; rather, we relied on a modified MacNab outcome measure. However, we have attempted to define the outcome categories clearly and to indicate specifically which, if any, symptoms or deficits remained after surgery.

Conclusions

TMED is a safe and effective surgical approach for the treatment of lateral and noncalcified ventral thoracic disk herniations that avoids entering the chest and avoids the need for thoracic fusion. Operative time, blood loss, and length of hospital stay compare favorably with other approaches. Although TMED is easy to perform and can be done quickly and safely with practice, this procedure should be performed only after gaining adequate endoscopic training.

References are available online at www.rush.edu/neurosciencereview.
Manual Aspiration Technique to Retrieve a Prematurely Detached Coil During Cerebral Aneurysm Embolization

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Introduction

The indications for endovascular treatment of intracranial vascular pathologies continue to expand as new techniques and technologies evolve. This trend in turn has increased both the number of endovascular procedures performed and a proportional number of procedure-related complications, including coil stretching, unraveling, prolapse, and migration. The reported incidence of coil stretching is less than 2%, and the incidence of coil protrusion and migration is only 0.5%.1,2 Despite the rare incidence of these coil complications, these events represent a challenge to manage. Loose coil ends significantly contribute to thromboembolic events, increasing risk of ischemic stroke and permanent neurologic deficit.3 Several devices and published technique strategies to retrieve loose coils are currently available. Each technique, however, is limited to specific complications and thus has limited efficacy.

We describe an alternative to these salvage strategies that may serve as a simple, elegant retrieval strategy in the limited situation where a Penumbra Coil 400 (Penumbra, Alameda, California) detaches prematurely inside of the PX 400 microcatheter (Penumbra, Alameda, California). In this specific situation, a stretched and detached coil trapped inside of a coil mass may be successfully retrieved using careful aspiration under direct fluoroscopic visualization. A case illustration using this aspiration technique is presented.

Case Illustration

A 59-year-old woman with hypertension and a family history significant for intracranial aneurysms presented for evaluation of an incidental basilar tip aneurysm found after a workup for dementia. The aneurysm had a maximum diameter of 11.8 mm

Figure 1. Anterior-posterior (A) and lateral (B) 3-dimensional reconstruction views of a digital subtraction angiogram depicting an incidentally discovered basilar tip aneurysm.

Figure 2. A, Anterior-posterior fluoroscopic view of the basilar tip aneurysm filled with a coil mass. B through D, Sequential fluoroscopy frames showing release of the detached, partially deployed coil from the coil mass during aspiration through the PX 400 microcatheter. The white arrows identify the distal end of the loose coil.
Discussion

Premature coil detachment occurs when a pusher wire is no longer connected to a coil during an embolization procedure. Despite the varied coil detachment mechanisms available, including mechanical, hydraulic, electrothermal, and the classic electrolytic, premature detachment continues to be a potential technical complication, though its occurrence is rare. Excessive force applied to a coil through repeated coil deployments or navigation through tortuous vascular anatomy increases the chance of premature detachment. If a coil partially deployed into an aneurysm prematurely detaches while inside of the delivery catheter, that is, if the proximal end of the coil remains in the microcatheter, then the disconnected pusher wire may still be used to completely deploy the coil into the aneurysm. In the case illustration presented, this technique was attempted, but the remaining portion of the coil was not accepted into the coil mass within the aneurysm without microcatheter kickback outside of the aneurysm. In this situation, salvage strategies must be considered to avoid the potential complications of a loose coil, including distal embolization, ischemic stroke, and permanent neurologic deficit.

A coil that prematurely detaches from a pusher wire while completely outside the delivery microcatheter is a difficult problem to manage because control over the coil is lost completely. The proximal portion of the coil in this situation is a loose end, and the entire coil may be loose if the distal end was not yet partially delivered into a coil mass. Several strategies to manage this situation have been published. First, stents have been deployed over loose coil ends, securing the loose ends against the lumen with favorable success in limited cases. Balloon remodeling techniques, in which a balloon is placed at the base of the aneurysm neck, compacting the coil mass inside the aneurysm and assisting the placement of a prolapsed coil loop back into the aneurysm, have also been described. Several types of snares and alligator clamps are also available to retrieve loose, detached coils. However, the risks of coil retrieval using these devices, for example, thromboembolism and damage to the intima, must be weighed against the risks of other management strategies. Capturing a loose coil with a snare is a very difficult maneuver, and contralateral groin access is typically required. A technique using a balloon to stabilize a coil mass while a snare was used to retrieve a loose coil has been described. Several reports describe an alternative strategy to retrieve a loose coil using the Merci Retrieval System (Concentric Medical, Inc, Mountain View, California) or thrombectomy stent devices. Ultimately, if attempts at retrieval of a loose coil are unsuccessful in the presence of compromised distal blood flow, open surgical procedures have been used to remove displaced coils.

Some control over a coil is retained when the proximal end of a prematurely detached coil remains inside of the delivery microcatheter. It may be possible to complete the deployment of a coil that was partially deployed into an aneurysm in this circumstance, particularly if the position of the microcatheter remains inside the aneurysm despite the fact that the pusher wire is no longer physically attached to the coil. In addition to the

Figure 3. Photograph of the syringe connected to the PX 400 microcatheter depicting the prematurely detached coil within the catheter hub after aspiration retrieval.

and a 5.8-mm neck (Figure 1). The patient ultimately consented to an elective stent-assisted coil embolization of the aneurysm. On the day of the procedure, the patient was sedated and intubated without complication, and her right femoral artery was accessed. Her intracranial vascular anatomy was characterized with digital subtraction angiography. Through a 6F Neuron guide catheter (Penumbra, Alameda, California) placed into the left vertebral artery, a Prowler Select Plus microcatheter (Cordis Corporation, Bridgewater, New Jersey) was navigated into the left posterior cerebral artery. A 4.5×22-mm Enterprise stent (Cordis Neurovascular, Miami, Florida) was deployed across the neck of the aneurysm from the left P1 segment to the basilar artery. The aneurysm was then accessed with a 0.025-inch inner diameter PX 400 microcatheter with a standard microwire through the struts of the stent and a Penumbra Coil 400 was deployed, framing the aneurysm dome. A second coil was passed through the same microcatheter in an attempt to fill the aneurysm, but only half of the coil could be inserted into the dome without causing coil loop prolapse. The microcatheter fell out of the aneurysm, but the distal end of the coil remained trapped in the coil mass. Attempts to completely deploy the coil into the aneurysm were unsuccessful. After attempts to retrieve the coil were made, it eventually prematurely detached from the pusher wire, leaving the proximal portion of the partially deployed coil still inside the microcatheter.

At this point of the procedure, options of placing a second stent to secure the loose coil end against the vascular lumen or using a snare to attempt coil retrieval were considered. As an alternative, the PX 400 microcatheter was detached from continuous flush and the pusher wire was withdrawn. A 20-mL syringe was then fixed to the microcatheter, and with careful aspiration under fluoroscopic visualization, the detached coil was retrieved through the microcatheter, disengaging it from aneurysm coil mass without disruption (Figure 2). The loose coil was clearly visualized inside of the hub of the microcatheter after the aspiration retrieval (Figure 3). Subsequent coils were delivered into the microcatheter, occluding the aneurysm without further complication. No contrast extravasation was appreciated during the procedure, and the patient’s neurologic examination afterward was unchanged relative to her examination prior to the procedure.
salvage strategies available for a proximal coil end that was prematurely detached outside of the delivery catheter, a prematurely detached proximal coil end that is retained in a microcatheter offers more retrieval strategies. The delivery microcatheter, for instance, can be used as a guide to slide a snare down to and around the loose coil end. A strategy for wedging the loose coil end inside of the microcatheter using guidewires has been described. Ng et al described retrieving a prematurely detached coil that remained inside of a microcatheter using a vacuum inside of the microcatheter created by rapidly withdrawing the pusher wire. It has also been suggested that a vacuum can be created to retrieve a loose coil in this manner by attaching a syringe to the hub of the microcatheter, though a report of this technique has not been published. We report the successful application of this technique to retrieve a prematurely detached coil that partially remained inside of the delivery microcatheter.

The design features of the Penumbra Coil 400 used in the case illustration may have aided the aspiration retrieval of the coil. This coil has a relatively larger primary diameter and thin inner filament wire, making the coil very pliable and soft. We postulate that the combination of coil softness and larger size may have enabled the complete aspiration retrieval of this coil through the microcatheter. The microcatheter inner diameter and the coil size allow for a minimal free space between them. This design creates an optimal seal, allowing for increased vacuum power during manual aspiration. The coil softness and vacuum created from the tight fit contributed to such a dramatic migration of the coil from the aneurysm to the aspirating syringe on the hub of the microcatheter. We have not tested the manual aspiration coil retrieval method with different types of coils and microcatheters. This technique was helpful in this case because the PX 400 microcatheter was inside of a 6F guide catheter. This setup left no room for our preferred method of coil retrieval using the microcatheter as a guide to slide a snare down to and around the loose coil end. The technique described allowed for a very simple bailout from a potentially difficult situation.

Conclusion

Premature coil detachment is a difficult complication to manage and significantly contributes to thromboembolic events, thus requiring either retrieval or fixation of the prolapsed coil. Optimal salvage strategies must be tailored to the specific situation and the experience of the interventionist. We describe an effective, safe technique for retrieving a prematurely detached Penumbra coil that remains in the delivery microcatheter.

References are available online at www.rush.edu/neuroscincereview.
Diffusion Tensor Imaging of Parkinson Disease, Atypical Parkinsonism, and Essential Tremor

Janey Prodoehl, PhD; Hong Li, PhD; Peggy J. Planetta, PhD; Christopher G. Goetz, MD; Kathleen M. Shannon, MD; Ruth Tangonan; Cynthia L. Comella, MD; Tanya Simuni, MD; Xiaohong Joe Zhou, PhD; Sue Leurgans, PhD; Daniel M. Corcos, PhD; David E. Vaillancourt, PhD

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The diagnosis of Parkinson disease (PD) in the early stages can be challenging because symptoms often overlap with other movement disorders, such as the parkinsonian variant of multiple system atrophy (MSAp), progressive supranuclear palsy (PSP), and essential tremor (ET). Advances in neuroimaging have led to a greater understanding of which brain regions are affected in these movement disorders, with the basal ganglia and regions of the cerebellum commonly implicated. Using diffusion tensor imaging (DTI), several laboratories have confirmed that fractional anisotropy (FA) in the substantia nigra is reduced in participants with PD compared with control participants. ET and PD participants have different FA patterns in the dentate nucleus and superior cerebellar peduncle. DTI has also shown promise for differentiating PD from atypical parkinsonism. Diffusion-weighted imaging has been used to discriminate MSAp from PD and healthy controls on the basis of putaminal and pallidal diffusion coefficients. However, in other studies this same technique has shown mixed results for distinguishing participants with PSP from those with MSAp. In a recent study, regional apparent diffusion coefficients calculated from multiple brain regions, including the basal ganglia, thalamus, brainstem, and cerebellum, were shown to differentiate MSAp (primarily the cerebellar subtype), PSP, PD, and healthy control participants at the group level, but receiver operating characteristic (ROC) curves were not reported, and apparent diffusion coefficients from multiple brain regions were not combined to help improve group classification. Despite the promise that DTI has for understanding structural differences across movement disorders, the literature still lacks a robust method that distinguishes PD, MSAp, PSP, ET, and control participants using the same technique in 1 study.

Rather than evaluating early-stage patients when the differential diagnosis may be challenging, the current study evaluated patients with PD, MSAp, PSP, and ET when the diagnoses had reached probable criteria, with the future goal of evaluating patients using the methodology developed in this article at an earlier disease stage. In particular, we extracted multiple DTI measures from multiple basal ganglia and cerebellar regions known to be affected in these movement disorders. We performed a series of analyses on these data to evaluate how well DTI distinguishes between movement disorders in comparisons that have clinical importance. The goal was to determine if DTI can distinguish (1) movement disorder (PD, MSAp, PSP, ET) from control, (2) parkinsonism (PD, MSAp, PSP) from control, (3) PD from atypical parkinsonism (MSAp and PSP), (4) PD from MSAp, (5) PD from PSP, (6) MSAp from PSP, and (7) PD from ET.

Patients and Methods

Participants

Seventy-two patients participated between 2009 and 2011 (PD, 15; MSAp, 14; PSP, 12; ET, 14; control, 17). Patients were diagnosed by movement disorder specialists at Rush University Medical Center or Northwestern University using the following criteria: diagnosis of PD based on UK Parkinson’s Disease Society Brain Bank criteria, probable MSAp based on American...
Academy of Neurology and American Autonomic Society criteria, probable PSP based on NINDS-SPSP (National Institute of Neurological Disorders and the Society for Progressive Supranuclear Palsy) criteria, and ET based on the statement of the Movement Disorder Society. Diagnosis of all patients was reconfirmed 18 months after DTI by reviewing patient charts. Clinical features of the PSP patients were consistent with the Steele-Richardson-Olszewski subtype rather than the PSP-parkinsonism (PSP-P) subtype. The controls were healthy volunteers who did not have a history of neurological or psychiatric disease. Patient and control group summary characteristics are given in Table 1. PD, MSAP, and PSP participants were matched at inclusion on the basis of UPDRS-III (Unified Parkinson Disease Rating Scale, part III) scores. More detailed UPDRS motor scores are included in Appendix e-1 (Supporting Information) along with medications each participant was taking when enrolled in the study. Because the effects of medication on DTI are not known, we tested all participants after overnight withdrawal from antitremor and antiparkinsonian medications. Participants gave written informed consent.

### DTI Acquisition

Data were acquired on a GE 3.0-Tesla Sigma HDx scanner using a customized DTI pulse sequence that corrects for eddy current–induced distortion. Images were acquired using an 8-channel phased-array head coil. The data acquisition parameters were as follows: TR, 4500 ms; TE, 82 ms; b = 0; 1000 s/mm²; diffusion gradient directions, 27; FOV, 200 mm²; k-space matrix, 192 × 128; image space matrix, 256 × 256 (image interpolation was done using a homodyne reconstruction method); NEX, 4; slice thickness, 4 mm; slice skip, 1 mm; and slice number, 15. Two scans were performed to cover the basal ganglia and cerebellum. In the first, the top slice was placed in the axial plane approximately 4 mm superior to the corpus callosum. In the second, the bottom slice was placed in the axial plane approximately 4 mm below the bottom of the cerebellum.

### DTI Analysis

All diffusion tensor calculations were carried out using DtiStudio. Images were inspected for artifacts related to eddy currents and motion. Eddy current distortion was properly corrected in the customized pulse sequence. AFNI software was used to quantify head motion, which was within 1 mm for all participants. We did not exclude any data. We calculated 4 DTI measures to use in classification: (1) FA, a measure of diffusion anisotropy; (2) radial diffusivity (RD), the average diffusivity of the 2 nonprincipal eigenvalues of the diffusion tensor; (3) longitudinal diffusivity (LD), diffusivity corresponding to the principal eigenvector; and (4) mean diffusivity (MD), the average of all 3 eigenvalues of the diffusion tensor.

Regions of interest (ROIs) were selected on the basis of previous pathological and neuroimaging findings in these movement disorders. Figure 1 shows the B0 (b = 0) images and color maps of relevant slices for the basal ganglia and red nucleus (Figure 1A) and cerebellum (Figure 1B) to illustrate the number and location of ROIs. All ROIs were circular and drawn bilaterally. Data were averaged across sides because we did not observe laterality effects. Because each structure has a unique size and subcomponents exist within the various structures, ROIs were drawn to match the size of each structure. Three ROIs of 5 voxels in diameter were drawn in the caudate, putamen, and globus pallidus. The FA image was used to visualize the external capsule, and the putaminal ROIs were placed immediately medial to it. In the red nucleus, 1 ROI (4 voxels in diameter) was placed, and in the substantia nigra 3 ROIs (4 voxels in diameter) were placed, consistent with previous work. In the cerebellum, ROIs were drawn with reference to the color map: 2 ROIs (3 voxels in diameter) were placed in the superior cerebellar peduncle, 2 ROIs (6 voxels in diameter) were placed in the middle cerebellar peduncle, and 1 ROI (3 voxels in diameter) was placed in the inferior cerebellar peduncle. Three ROIs in the dentate nucleus (5 voxels in diameter) were drawn with reference to the B0 image. The combination of FA, RD, LD, and MD measures in each of the 21 ROIs yielded a total of 84 variables.

A standard noise threshold was set within DtiStudio to create a mask for the diffusion tensor calculations, and each image was visually inspected to ensure that signal loss did not occur in the ROIs or in surrounding tissue. All ROIs were drawn blinded to group status by an experienced investigator on the basis of the

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**Figure 1.** Region-of-interest (ROI) drawings for the basal ganglia and cerebellum. A, Three images from the diffusion tensor imaging (DTI) analysis: B0 (b = 0) image (analogous to T2-weighted image), fractional anisotropy (FA) map, and color map. These images were used to draw ROIs in the caudate nucleus (red circles), putamen (white circles), globus pallidus (yellow circles), substantia nigra (green circles), and red nucleus (blue circles). The ROIs were always placed on the image, where the structure can be viewed. All 4 DTI measures were extracted from each ROI. B, Same image type as part A including B0 image, FA map, and color map. ROIs are shown in the superior cerebellar peduncle (red circles), middle cerebellar peduncle (white circles), inferior cerebellar peduncle (yellow circles), and dentate nucleus (green circles). Note that the ROIs for the peduncles were drawn on the color map, whereas the dentate ROIs were drawn on the B0 image.
methods described above. A separate individual, also blinded to diagnosis, extracted the DTI measures for each ROI. To determine interrater reliability, a third trained person, again blind to diagnosis, drew ROIs on 5 randomly selected participants per group.

Statistics

We performed ROC analyses for comparisons between groups using custom C++ code based on the ROC analysis approach. We compared control versus movement disorder (PD, MSAp, PSP, ET), control versus parkinsonism (PD, MSAp, PSP), PD versus parkinsonism (MSAp, PSP), PD versus MSAp, PD versus PSP, MSAp versus PSP, and PD versus ET. The ROC analysis selected the top-ranked variables associated with the disease classification by maximizing the area under the curve (AUC, which measures the accuracy of a test in correctly identifying participants with the targeted condition) using the classification probabilities estimated from the logistic regression as an input. A forward selection procedure was used, examining 1 variable at a time. Selection was started with the variable that gave the highest AUC, and then each of the remaining variables was added into the logistic model to estimate the classification probabilities. The second variable selected was the variable that gave the highest AUC together with the first variable. The number of selected top-ranked variables was chosen to be less than 10% of the combined number of participants for each model classification to ensure stable estimates. The numbers of variables for the comparisons were 7 for control versus movement disorder, 6 for control versus parkinsonism, 4 for PD versus parkinsonism, 3 for PD versus MSAp, and 2 each for PD versus PSP, MSAp versus PSP, and PD versus ET. The set of DTI measures that gave the highest AUC is reported for each model. Sensitivity and specificity were quantified for each model for each comparison. Intraclass correlation coefficients were obtained from a 2-way mixed model to quantify interrater reliability of experienced and novice ROI drawers.

Results

Comparing Participant Characteristics

Neither the age of the participants nor the proportions of men and women differed significantly across groups (Table 1). Years since first reported symptom differed significantly across the 4 patient groups. Because this variable was significant, we included this variable in the ROC analysis to determine if it was a predictor of disease group. The UPDRS-III scores did not differ across groups with parkinsonism.

Distinguishing Patients From Healthy Controls

Figure 2 and Table e-3 provide a summary of the classification models described below. The first step of the analysis was to determine how well the DTI measures distinguished the disease state from control. Participants with PD, MSAp, PSP, and ET were included as 1 group, and DTI measures in this combined group were compared against DTI in the healthy control group. The AUC was 0.98 (sensitivity, 92%; specificity, 88%) in this comparison, with 7 diffusion variables identified in the caudate, pallidum, substantia nigra, red nucleus, and middle and inferior cerebellar peduncles. Comparing

<table>
<thead>
<tr>
<th>Group analysis</th>
<th>AUC</th>
<th>Sen</th>
<th>Spec</th>
<th>Caudate</th>
<th>Putamen</th>
<th>GP</th>
<th>SN</th>
<th>RN</th>
<th>SCP</th>
<th>MCP</th>
<th>ICP</th>
<th>Dentate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control vs. ET/MSAp/PSP</td>
<td>0.98</td>
<td>92%</td>
<td>88%</td>
<td>FA₂</td>
<td>RD₂</td>
<td>FA₁</td>
<td>FA₂</td>
<td>LD₁</td>
<td>RD₁</td>
<td>RD₁</td>
<td>FA₂</td>
<td>R₁</td>
</tr>
<tr>
<td>Control vs. PD/MSAp/PSP</td>
<td>0.99</td>
<td>93%</td>
<td>91%</td>
<td>FA₁</td>
<td>RD₂</td>
<td>LD₁</td>
<td>RD₁</td>
<td>MD₁</td>
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<tr>
<td>PD vs. MSAp/PSP</td>
<td>0.99</td>
<td>90%</td>
<td>100%</td>
<td>LD₁</td>
<td>LD₁</td>
<td>FA₃</td>
<td>FA₃</td>
<td>MD₁</td>
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<tr>
<td>PD vs. MSAp</td>
<td>0.99</td>
<td>94%</td>
<td>100%</td>
<td>FA₃</td>
<td>RD₂</td>
<td>RD₁</td>
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<tr>
<td>PD vs. PSP</td>
<td>0.96</td>
<td>87%</td>
<td>100%</td>
<td>LD₁</td>
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<tr>
<td>MSAp vs. PSP</td>
<td>0.97</td>
<td>90%</td>
<td>100%</td>
<td>FA₃</td>
<td>RD₁</td>
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<tr>
<td>PD vs. ET</td>
<td>0.96</td>
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Abbreviations: FA, fractional anisotropy; LD, longitudinal diffusivity; MD, mean diffusivity; RD, radial diffusivity.

Figure 2. Findings from logistic regression and receiver operating characteristic (ROC) analyses. Area under the curve (AUC) was the primary outcome variable in the study and is reported for each comparison. Sensitivity (Sen) and specificity (Spec) are also shown. Dark gray indicates regions of the brain included in each comparison. The dependent measures included for each comparison are listed in each dark gray box. Subscript identifies the ROI number for each region (1, anterior; 2, middle; 3, posterior).
participants with parkinsonism (PD, MSAp, and PSP) with healthy controls, the AUC increased to 0.99 (sensitivity, 93%; specificity, 91%) using DTI measures from the putamen, pallidum, substantia nigra, red nucleus, and middle cerebellar peduncle.

**Distinguishing PD From Atypical Parkinsonism**

To determine how well the DTI measures distinguished PD from atypical parkinsonism, MSAp and PSP were pooled, and the DTI measures in this combined group were compared with DTI measures in the PD group. In this comparison, the AUC was 0.99 (sensitivity, 90%; specificity, 100%) using DTI measures from 3 ROIs: putamen, substantia nigra, and dentate nucleus.

**Distinguishing Between Parkinsonian Groups**

The next step of analysis was to determine how well the DTI measures separated the 3 types of parkinsonism from each other: PD from MSAp, PD from PSP, and MSAp from PSP. The AUC was 0.99 (sensitivity, 94%; specificity, 100%) for PD versus MSAp using DTI measures from the substantia nigra and middle cerebellar peduncle. For PD versus PSP, the AUC was 0.96 (sensitivity, 87%; specificity, 100%) using DTI measures from the putamen and substantia nigra. To distinguish MSAp from PSP, the AUC was 0.97 (sensitivity, 90%; specificity, 100%) using DTI measures from the caudate and middle cerebellar peduncle.

**Distinguishing PD From ET**

The final step of analysis was to determine how well the DTI measures distinguished PD from ET. The AUC was 0.96 (sensitivity, 92%; specificity, 87%) using DTI measures from the caudate and substantia nigra.

**Interrater Reliability**

Intraclass correlations of FA values for the basal ganglia, red nucleus, and cerebellum between the experienced ROI drawer and the novice ROI drawer were all above 0.90.

**Discussion**

This study is the first to combine multiple DTI measures and target regions in the basal ganglia, red nucleus, and cerebellum to provide accurate classification of individual participants with PD, MSAp, PSP, and ET. Figure 2 provides a road map differentiating the movement disorders on the basis of specific brain regions and dependent measures needed in each group classification. This multitarget approach yielded consistent targets in the caudate, putamen, globus pallidus, substantia nigra, red nucleus, and middle cerebellar peduncle across the different participant group comparisons. A key point is that the pattern of DTI targets and measures that yielded the highest AUC for differentiating these movement disorders was unique for each classification. It is also important to emphasize that we were interested in which combination of brain areas and DTI measures provided the best classification of the groups. Therefore, areas beyond those that provided the best classification could still be affected by the diseases.

Pathologically, there is substantial cell loss in the substantia nigra of PD as well as MSAp and PSP, but not ET.22,37 We showed that FA and RD from the substantia nigra were DTI measures that were essential in most group classifications. The administration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in a murine model of PD demonstrated that these same measures derived from DTI increased (RD and LD) or decreased (FA) within 7 days following MPTP administration.22,37 The findings (Table e-3) confirm the findings of previous studies from various laboratories that FA is reduced in the substantia nigra of PD patients compared with control participants.5,9,39

Most importantly, the findings demonstrate that DTI of the substantia nigra is insufficient to differentiate PD from these other movement disorders, even though it is a critical variable that was included in all but 1 of the classifications of Figure 2. Additional regions that improved the classification model in Figure 2 were the caudate; putamen; globus pallidus; red nucleus; superior, middle, and inferior cerebellar peduncles; and dentate nucleus.

Instead of combining measures across multiple targets, most previous studies have focused on selected regions when comparing atypical parkinsonism with PD. Three areas that have shown promise are the putamen, pallidum, and pons, which are known to degenerate in MSAp.12 Trace values from the putamen and pallidum have been shown to be increased and FA values in the pons decreased in MSAp compared with controls and participants with PD.12 When distinguishing 9 MSAp participants from 9 PD participants, trace values (equivalent to mean diffusivity) from the putamen revealed an AUC of 1.0.13 Further, sensitivity and specificity for FA values were 70% and 100%, respectively, in the pons and 70% and 87.5%, respectively, in the putamen to differentiate 10 MSAp patients from 21 PD patients.40 Importantly, these authors suggested that FA values and apparent diffusion coefficients considered together provide better classification than just 1 measure alone. Our results support this. Although the present study did not identify the putamen as a region for distinguishing MSAp from PD, our results identified the putamen as an important ROI when comparing control versus PD, MSAp, and PSP, PD versus MSAp and PSP, and PD versus PSP. Also, measures from the pallidum were included in our classification for control versus PD/MSAp/PSP/ET and control versus PD, MSAp, and PSP, which is in agreement with previous work, indicating the importance of DTI measures from the pallidum.31

The aforementioned analyses were performed in gray matter regions, including the substantia nigra, putamen, and globus pallidus. Although these areas are not the typical targets for DTI studies, gray matter diffusion anisotropy changes have been reported in brain maturation,41 aging,42 and other neurological disorders.43 The underlying mechanism for such change has not been understood as thoroughly as white matter changes, and future studies are needed to explore this important area.

In this study, we have also examined changes in diffusion parameters in white matter. Within the cerebellum, diffusion-weighted imaging has shown that the apparent diffusion
coefficient from the superior cerebellar peduncle provides accurate classification of PSP versus PD\textsuperscript{15,44} and of PSP versus MSAp.\textsuperscript{15} Our analytic approach examined all 4 DTI measures from all ROIs. At each iteration, the brain target and measure with the strongest classification were included on the basis of the AUC. With this approach, a promising ROI might have been left out because another region had a slightly greater AUC. This was the case for the superior cerebellar peduncle in the comparison of PD with PSP. In this contrast, the first variable was FA from the substantia nigra, and the second variable was longitudinal diffusivity from the putamen, providing an AUC of 0.96. If we included FA from both the substantia nigra and superior cerebellar peduncle, the AUC would have been equal to 0.94, which, although still good, was not the highest AUC possible. Our findings are consistent with postmortem studies that have demonstrated that the basal ganglia and superior cerebellar peduncle are affected by neurodegeneration in PSP.\textsuperscript{30,31} To maintain stability in the parameter estimates in the logistic regression, the number of variables was constrained to 10% of the number of participants in each comparison.\textsuperscript{36} Thus, future work with larger sample sizes could identify additional brain targets and DTI measures using this approach. In addition, the multiparametric approach can be further extended to other diffusion imaging parameters obtained from not only the diffusion tensor model but also other advanced diffusion models for brain tissue.

The current study has several important caveats. Each participant was diagnosed by neurologists who specialize in movement disorders using probable diagnostic criteria, the highest level of diagnostic certainty short of autopsy confirmation. Although studies indicate that such a diagnosis for PD and atypical Parkinsonism has high sensitivity and specificity when performed by a neurologist specializing in movement disorders,\textsuperscript{5} the findings may have been different if we could have based the diagnosis on future neuropathology. Further, our sensitivity and specificity findings may not apply when the diagnosis is less certain, and this point is a focus of future studies. Finally, the current study focused on the basal ganglia and cerebellum. Including targets in the pons could prove useful for classifying MSAp, and including targets in the cortex could prove important for differentiating MSAp, PD, PSP, and ET, particularly in later stages. Although not the same technique, recent network approaches with metabolic imaging have proven beneficial by combining data from the cortex in distinguishing PD, MSAp, and PSP.\textsuperscript{45}

In summary, the current findings demonstrate that multiple DTI measures from multiple targets in the basal ganglia, red nucleus, and cerebellum accurately classify control participants and patients with PD, MSAp, PSP, and ET. If these findings are replicated in a larger cohort across multiple sites, this readily available approach may have utility outside specialized research centers.

References are available online at www.rush.edu/neurosciencereview.
Select publications (2013)*

Departments of Neurological Sciences and Neurological Surgery


*Clinicians from Rush University Medical Center are indicated in bold.


Fleischman DA, Yu L, Arfanakis K, Han SD, Barnes LL, Arvanitakis Z, Boyle PA, Bennett DA. Faster cognitive decline in the years prior to MR imaging is associated with smaller hippocampal volumes in cognitively healthy older persons. Front Aging Neurosci. 2013;5:


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- Community-Based End-of-Life Intervention for African-American Dementia Caregivers
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- Effect on Cognition in Patients With Parkinson's Disease

**Deborah Hall, MD, PhD**
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- Adult Neurological Phenotypes of Fragile X Gray Zone Expansion
- Genetic and Environmental Risk Factors for Progressive Supranuclear Palsy (PSP)
- Amount and Strength of New Bone Formation in a Canine Model

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- Developing a Human Embryonic Stem Cell Derived Dopamine Neuron Source for Cell Therapy in Parkinson's Disease

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- Validation of the Visual Analog Motion Scale
Volume and Quality Data

Neurology volumes*, fiscal years 2009-2013

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of discharges</th>
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*Includes neuro-oncology discharges

Rush had the second highest volume of neurology discharges in the Chicago region for fiscal years 2009-2013.

Neurology outpatient visits, fiscal years 2009-2013

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<th>Year</th>
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Neurological surgery outpatient visits, fiscal years 2009-2013

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*Includes all non-spine procedures

Volume of patients monitored for epilepsy for seizure classification or localization, calendar years 2009-2013

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<th>Year</th>
<th>Number of video EEG monitoring cases</th>
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Neurological surgery mortality o/e, fiscal years 2009-2013

<table>
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<th>Year</th>
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<tr>
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<td>2013</td>
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Source: University HealthSystem Consortium clinical database

Neurology mortality o/e, fiscal years 2009-2013

<table>
<thead>
<tr>
<th>Year</th>
<th>Mortality index</th>
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</tr>
<tr>
<td>2013</td>
<td>0.77</td>
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Source: University HealthSystem Consortium clinical database
Rush had the highest volume of neurosurgery discharges in the Chicago region for fiscal years 2011-2013.

**Neurological surgery volume of major cases by area, fiscal year 2013**

- **Spine and nerves**: 829 (29.45%)
- **Other**: 58 (2.06%)
- **Neuroendovascular-diagnostic**: 511 (18.15%)
- **Neuroendovascular-interventional**: 327 (11.62%)
- **Epilepsy and movement disorders**: 185 (6.57%)
- **Brain tumor**: 482 (17.12%)
- **Cerebrospinal fluid treatments**: 183 (6.50%)
- **Open cerebrovascular**: 75 (2.66%)
- **Functional**: 41 (1.46%)
- **Trauma**: 124 (4.41%)
- **Strokes**: Total: 930 cases
  - **Intracerebral hemorrhage**: 266 (28.60%)
  - **Ischemic stroke**: 470 (50.54%)
  - **Subarachnoid hemorrhage**: 136 (14.62%)
  - **Transient ischemic attack (<24 hours)**: 58 (6.24%)
As founding president of the Neurocritical Care Society, Thomas Bleck, MD, has been instrumental in evolving the role of the neurointensivist in neurointensive care units. A graduate of Rush Medical College, Bleck had the opportunity to shape neurocritical care as the first neuroscience intensive care unit director at the University of Virginia, and as chairman of neurology at Evanston Northwestern Healthcare in Evanston, Ill.—before returning to Rush University Medical Center in 2009. Now the associate chief medical officer for critical care at Rush, Bleck works with a team of seven board-certified neurointensivists in one of the busiest neurointensive care units in the region.

He recently sat down with neurosurgical colleague Lorenzo Muñoz, MD, to discuss what creates a well-working ICU, as well as how he discovered he was “constitutionally” a neurointensivist.
Muñoz: You started your career as an epileptologist, correct?

Bleck: I did.

Muñoz: And then you eventually became, as we all very fortunately know, a neurointensivist. What was your path from one to the other?

Bleck: I actually started out thinking I would be a general internist. After about 2-and-a-half years of my medicine residency, I decided that I’d rather be a hospital physician of some sort. I had a choice between doing pulmonology—which was not really pulmonary critical care medicine then but just pulmonology—or doing neurology.

I decided that epilepsy was more interesting to me than COPD, so I did a neurology residency and an epilepsy fellowship. I then was essentially a full-time epileptologist until 1984 when Roger Bone [MD] came to Rush as the chief of medicine. And I think Roger was initially suspicious—Who’s this neurologist hanging around my intensive care unit?—but one day he called me in and said, you know, by constitution you’re an intensivist. You should just admit this and move on with your life.

Muñoz: What do you think made you constitutionally an intensivist?

Bleck: I think the main thing is: What’s your view of the world, and how do you approach sick people? Do you see someone who’s in extremis as the patient that you want to take care of and manage? Or do you see that as an indication to call somebody else for help?

I call for help all the time, and often I’ll get another doctor out of bed in the middle of the night. But the main thing is you’re not running away from someone who’s very ill. It’s also that you want to have the skills and knowledge to be able to manage the illness. And beyond that, you want to push knowledge to somewhere new, about how to do things better.

A little more than 20 years ago when I started doing this full-time, a lot of the people we take care of now, we weren’t able to save then. Now they come back to visit us.

So I guess the other thing that is different for me constitutionally is also having an interest in how to help families through a difficult time. We can’t always fix everything. We have to know where our limits are, and to help the patient’s family come to terms with the bad outcome or the death that we can’t prevent.

Muñoz: This is something that I have learned from your experience: to know when to push that patient, and to what end you’re going to push that patient. And what I’ve learned from you is that you have a talent to say, “We’re going to go this far with this patient because there’s a reasonable chance that we may obtain a reasonable outcome.” You will not pour technology and interventions on a patient just because we can.

Unfortunately that can be the case in medicine, certainly in neurocritical care. I always tell patients I can operate on anything. I can take anything out—but to what end?

People in the profession can become almost nihilist saying, “You know what? This is how it is for the patient, nothing we can do, too bad.” And also you can go the other way when you have—usually the younger physicians—who want to do absolutely everything in spite of what outcomes are reasonable.

And it’s been a great education for me to watch you strike that balance. That’s something that I’ve always watched very closely how you handle that. Because it’s something that I can either learn from your experience or I can spend another 15 years getting to where you are. I’d rather learn from your experience; it’s the quickest way.

Bleck: As you know, you will come by the unit in the morning, and we’ll discuss the person who came in last night, and what are the pros and cons of doing a particular intervention. And then we’ll decide whether to do it. It’s a real collaboration, not just I say one thing, and you say another.

Muñoz: That brings up my next question, which is what do you think are the key components of a well-working neurocritical care unit?

Bleck: I think the most important things are that it be viewed as multidisciplinary from the start: that you have to have good collaboration between neurocritical care, neurosurgery, neuroradiology, and anesthesia. Each neuro ICU is a little bit different. At Rush a lot of our neuro ICU house staff come from anesthesia. That’s not true everywhere. I think it makes the anesthesia house staff better doctors, and it also provides us neurocritical care specialists (and especially the neurology residents) with a somewhat different view of how to approach sick patients.

And as part of your neurosurgical training commitment for your house staff, again, we’re seeing a lot more interaction and people learning from each other and getting to understand each other better.

And nursing, of course, is a huge component of it. We have very good nurses here who came to the unit knowing that they were going to deal with this group of patients. The ones who stay with it really are excellent.

Muñoz: You’ve had multiple opportunities to collaborate with your neurosurgical colleagues. What is it about neurosurgery here at Rush that has been instrumental in having this wonderful unit?

Bleck: The neurosurgical folks we have here now in part grew up with the notion that there should be a bedside intensivist. Clearly one way in which I function is as your eyes and ears. Some things we intensivists are able to manage ourselves, some we need to discuss with neurosurgery to get your input, and some we need your technical skills.
The neuro ICU here at Rush is the most collaborative and most smoothly running one I've ever had the opportunity to see. The fact that we communicate well, that there's not rivalry between the different house staffs, that we're all one team and people are not afraid to ask each other for help: those are the things that really do it.

I think our neuroendovascular program here is constantly trying to push the envelope for what can be done for very challenging patients. That makes my life more exciting. I'm always learning from you guys, not just about the surgery but about different ways to manage disorders that I haven't been exposed to before, both in endovascular and in open neurosurgery. On the tumor side and the epilepsy side, there is fantastic surgery here.

Also, one of the things we focus on in the ICU here is the detection and management of seizures in critically ill patients. One of the nice things about being at Rush is that I'm also running the EEG lab, which means I have the opportunity to apply resources to those patients that might not be available elsewhere.

Muñoz: You were the founding president of the Neurocritical Care Society. What are your thoughts on the evolution of this specialty?
Bleck: When the group started, there were about 14 of us. This would be back in about 2002. Now there are about 1,400 members of this society.

The evolution of the specialty has really, I think, changed the way that people in neurology training see what their job is and what their career paths are. We've been very lucky to have substantial growth and generally very good collaboration with our surgical colleagues and with radiology and anesthesia.

Muñoz: I know that you started out here at Rush. Your career took you on a different path to Virginia, and now we're very fortunate that you are here again. What brought you back?
Bleck: The thing that brought me back to the Chicago area was that I reconnected with a friend from college. She and I decided to get married and were trying to figure out where to live. We'd both gone to Northwestern, so moving to the Evanston area was something we could agree on. I worked for a couple of years at Evanston Northwestern, and when the chance to come back to Rush came up, I took it.

Muñoz: What would you like your legacy to be?
Bleck: I think the most important thing to me—looking at what I've done and what time I have left doing this—is that I have helped establish neurocritical care as an entity. And I have had the opportunity to train a number of really wonderful fellows who are now off on their own and doing great things.
For a patient consultation or referral to a neurologist at Rush, please call (312) 942-4500.

For a neurosurgeon at Rush, call (312) 942-6644.

**RUSH’S HOSPITAL: DESIGNED AROUND THE PATIENT**

Rush’s hospital transforms medicine by focusing on one key element: quality patient care. That’s why hundreds of doctors, nurses and other clinicians, with input from patients and families, worked with architects to design our state-of-the-art hospital Tower, which opened in January 2012. One of the nation’s most advanced hospitals, the new hospital houses acute and critical care patients, as well as technologically sophisticated surgical, diagnostic, and therapeutic services.

Photography provided by the Rush Photo Group and Kevin Horan.