FROM THE EDITOR

Dear Colleague,

I welcome you to this inaugural issue of the University Hospitals Neurological Institute Journal. It is our intention to provide you with a responsive forum for communicating timely and relevant information about advances in the basic sciences and clinical care of patients with neurological disorders. As a sign of our commitment to education, research and clinical care, we have provided an opportunity for you to assess yourselves after reading each article and to simultaneously receive appropriate credits for your Continuing Medical Education.

We wish to convey to you our excitement with the rapid transformation of clinical practice and research efforts under way here at the Neurological Institute at University Hospitals. Our systematic integration of personnel and programs dealing with neurological disorders has already brought about revolutionary changes in the way we collaboratively approach clinical care, basic and translational research efforts, and the education of neurological care providers. The very process of crafting this novel approach to an integrated Neurological Institute has brought with it a real enthusiasm for reaching out to address the concerns of our patients and colleagues.

We at the University Hospitals Neurological Institute Journal intend to provide you with timely and useful medical updates regarding neurological diseases and their treatment, a vehicle for self-assessment and acquiring CME credits, information about the exciting new developments at the University Hospitals Neurological Institute, and a forum for you to interact with us so that we might better serve you.

We appreciate the time you spend perusing the journal, and welcome any suggestions you may have to help shape the publication. Should you need further information about any of the topics in this issue, or to discuss the management of a particular patient, please don’t hesitate to contact us.

We value your support, and invite you to come join with us, and share the excitement surrounding the University Hospitals Neurological Institute.

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Immunotherapy for Brain Tumors: New Hope with Minimal Toxicity

By Andrew E. Sloan, M.D., FACS

Gliomas are the most common type of primary brain tumor. The incidence of primary brain tumors in the United States is about 15,800 per year, with approximately 10,000 deaths per year (CBTRUS, 2004), and they are the most common solid tumors in children. Malignant gliomas, which include anaplastic astrocytoma (AA) and glioblastoma multiforme (GBM) (grades III and IV, respectively), are the most common types of gliomas. Unfortunately, despite active clinical research over the last three decades, median survival of patients with GBM in most large studies remains less than one year.

Diagnosis and Treatment

The mainstay of treatment for newly diagnosed GBMs has been surgical resection and, until recently, the efficacy of radiation and chemotherapy has been poor. Radiotherapy extends median survival in GBM from three or four months to about 11 months. Traditional chemotherapy adds only modestly to that. However, a recent European study demonstrated that addition of concurrent temozolomide (TMZ) to conventional radiotherapy followed by post-radiation TMZ further increases median survival to 14.6 months, and more than 25% survive two years or more.1 However, with all these regimens, tumors inevitably recur locally, which is thought to reflect microscopic tumor diffusely infiltrating the brain prior to diagnosis (Figure 1). “Local control” can be achieved by surgery and radiotherapy and is effective in relieving mass effect as well as facilitating tolerance for adjuvant treatment. However, tumor recurrence is inevitable.

Alternative Modalities

The failure of conventional treatments has led to interest in alternative treatment modalities. Immunotherapy is particularly appealing for the treatment of gliomas due to the potential specificity of the immune response to eradicate deeply infiltrating residual tumor without damaging surrounding brain. The brain has long been considered “immunologically privileged” due to its lack of lymphatic drainage, low levels of immune co-stimulatory molecules, and the blood-brain barrier which limits the flow of cells and large molecules. However, recent studies suggest that this “privileged” status is relative rather than absolute. It has long been known that activated T-lymphocytes can penetrate the blood-brain barrier and perform immune surveillance (Figure 2). Indeed, the damage induced by multiple sclerosis and viral encephalitis is mediated by the inflammatory response.

Immunotherapy

Tumor vaccines have been under investigation for immunotherapy for melanoma and renal cell carcinoma for many years and have more recently been used for the treatment of other types of cancer, including malignant gliomas. Recent studies have demonstrated that vaccines may augment chemotherapy.

Immunotherapy can be divided into three types: passive, active and adoptive.2 Passive immunotherapy shortcuts the patient’s immune response by infusing an immune product, usually antibodies, interferons or cytokines. There are no recent studies demonstrating the efficacy of passive immunotherapy in the treatment of gliomas.

In contrast, the goal of active immunotherapy is to induce an effective antitumor immune response in the patient herself/himself. The immune response is usually mediated by cytolytic T-lymphocytes (CTLs). The vaccine usually includes tumor-related molecules and an adjuvant, a non-specific enhancer of immune function. Most glioma vaccines to date have utilized on of two approaches: peptide vaccines or dendritic cell (DC) vaccines. There has been increasing interest in both peptide vaccines and DC-based vaccines for glioma in recent years and early results appear promising for both.

Peptide vaccines are made from peptides of tumor-associated antigens thought to be expressed uniquely by glioma compared to normal brain. Such vaccines are simple to administer and require little or no preservation of the patient’s own tumor. In addition, their immunological efficacy can be correlated precisely by immunological monitoring. However, if an antigen-negative tumor variant emerges, the vaccine would likely be ineffective due to immune escape.

Dendritic cells are “professional” antigen-presenting cells capable of presenting multiple tumor antigens simultaneously (Figure 3). While they can be used to present small numbers of antigenic peptides, they are typically used to deliver a multivalent vaccine comprised of whole tumor cell lysate, making antigen escape less inevitable.

The Brain Tumor Center cares for adults, infants, children and adolescents with benign and malignant tumors, including gliomas, astrocytomas, oligodendrogliomas, brain stem gliomas, certain skull-base tumors, glioblastomas, ependymomas, mixed gliomas, meningiomas, acoustic neuromas, and medulloblastomas.

BRAIN TUMOR CENTER
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The Brain Tumor Center offers a world-class level of care, combining the experience, expertise, technical abilities and resources of recognized authorities in the field. The center offers highly individualized treatment plans for each patient. Brain Tumor Center physicians collaborate with specialists from the renowned Ireland Cancer Center and Rainbow Babies & Children’s Hospital.

Advanced Imaging Techniques Improve Completeness and Safety of Surgery

T1 MRI with contrast shows large malignant brain tumor in left primary motor cortex in axial (A, D, G), coronal (B, E, H) and sagittal planes (C, F, I) (Figure 1). Diffusion tensor imaging (DTI) shows marked edema in entire left hemisphere with tumor shifting primary motor tracts inferiorly (green) and anteriorly (blue) (E,F). Image-guided axial (A, D, G), coronal (B, E, H) and sagittal planes (C, F, I). T2-weighted axial image (D) and T1 MRI with contrast shows large malignant brain tumor in left primary motor cortex in (E,F).

Figure 1 – In patients with glioma, microscopic glioma typically infiltrates deep into the brain far outside the border of the enhancing portion of the tumor seen on MRI. (Illustration courtesy of Dr. Christoph Pedain, BrainLAB.)

Figure 2 – The process of immunosurveillance begins when T-lymphocytes encounter tumor cells after leaving the blood vessel. T-lymphocytes then travel to lymph nodes where they encounter antigen-presenting cells, usually dendritic cells, and stimulate CD8 cytolytic T-cells (CTLs). The CTLs then return to the circulation and patrol the body for additional tumor cells.
New Trials at UH Neurological Institute

Two new trials being conducted at the Neurological Institute and Ireland Cancer Center, which have developed an evidence of an antitumor immune response.

The first case report of trigeminal neuralgia (TN) dates to 1671, when it proved fatal to the unfortunate Johannes Laurentius Bausch, a physician.1 Later works by Nicolaus Andre, John Fothergill and Charles Bell established “tic douloureux” as a clinical syndrome resulting from a disorder of the trigeminal nerve.2,3

The pain of trigeminal neuralgia is classically described as sharp, lancinating, electric shock-like, short lasting, intermittent and variable, and often so intense as to interfere with daily routines, speaking or even eating. The pain usually can be triggered by movement or by touching part of the face or mouth, giving rise to the term, “trigger point.” Any of the three branches of the trigeminal nerve may be affected, with V2 being the most common. Absence of pain between the attacks is typical, as are frequent remissions, often early in the course of the disease. Typically, the neurologic examination is either normal or demonstrates a subtle decrease in sensation in the affected distribution, perhaps indicating suppression of the ipsilateral corneal reflex. Atypical trigeminal neuralgia (ATN) encompasses the preceding, with the addition of a lesser component of more constant pain, perhaps in a broader distribution.1 Atypical face pain (AFP) is predominantly constant, and may not be confined to the trigeminal sensory distribution. Derangement dysesthesia, or anesthesia dolorosa (AD), is a constant, annoying, burning sensation in the distribution of the facial numbness that causes great suffering when it occurs as a result of denervation procedures.4

Many patients with typical idiopathic trigeminal neuralgia demonstrate complete resolution of the trigeminal nerve root at the pontine entry zone, termed the Obersteiner-Redlich zone of transition from central myelin to peripheral Schwann cell sheathing.5,6,7 This is most commonly caused by adjacent vessels, especially the superior cerebellar or anterior inferior cerebellar arteries, or the facial nerve itself.

Medical Treatment
Many varied treatments have been attempted to relieve the severe pain of TN. Phenytoin (Dilantin) became widely used in the 1950s to treat TN. Blom established in 1962 that carbamazepine (Tegretol) appeared more effective.11 More recently, the anticonvulsants clonazepam (Klonopin), oxcarbazepine (Trileptal), sodium valproate or valproic acid (Depakote) and gabapentin (Neurontin) have also been used successfully. The central muscle relaxant baclofen (Lioresal) has also been prescribed for TN. Medical therapy is the first line of defense whenever treating a patient with TN. Over 10 years of followup, however, only 56% of patients maintain satisfactory pain relief with

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(Trigeminal Neuralgia continued)

medical therapy. Occasionally, patients will not respond satisfactorily to sequential trials of medications, or they will experience sufficiently significant side effects to prevent them from benefiting from this form of therapy. Once medical therapy has been exhaustively attempted without success, the patient should be considered a candidate for surgical intervention. Numerous neurosurgical procedures have been developed and advocated for the treatment of medically refractory TN.

Trigeminal Nerve Section

Therapeutic sectioning of the trigeminal nerve root between the brainstem and the Gasserian ganglion was first reported by Sir Victor Horsley in 1891. He used an intradural subtemporal approach to the nerve. Krause and Hartley both subsequently reported their experience with an extradural subtemporal approach. Spiller and Frazier in 1901 described a middle fossa approach for dorsal root section that became popular. Stokey operated on 710 nerves for trigeminal neuralgia between 1925 and 1955. He achieved complete relief in 93%, and 87% remained without pain after 18 months. The mortality for this surgery was 1%. Facial numbness was encountered in 8%, and permanent in 1%. Keratitis resulted in 1%. Mild paresthesias were noted in 28%, with severe paresthesias in 10%.

In 1925, Walter Dandy described a posterior fossa approach for sectioning of the posterior sensory roots of the trigeminal nerve at the pons. This partial section of half of the sensory root sought to avoid loss of corneal sensation and resultant keratitis. The anterolateral motor nerve was left intact. Interestingly, Dandy noted a frequent association of an extracranial loop compressing and distorting the trigeminal nerve adjacent to the pons. In his series of 500 patients, Dandy reported that only 6% experienced recurrences. With the advent of microvascular decompression surgery, trigeminal rhizotomy has been reserved for those cases where a negative exploration is encountered, or where the trigeminal neuralgia has failed treatment with other surgeries. It is often presumed that multiple sclerosis or other neurodegenerative disorders are the etiology in such cases.

Bederson and Wilson reported on 252 patients in 1989. Excellent results were noted in 75% of good results in 8%, often at the price of more sensory loss and dysesthetic sequelae.

Partial section of the trigeminal nerve appears a useful surgical treatment for patients with negative explorations at microvascular decompression, for those with multiple sclerosis or neurodegenerative disorder, or those who have failed other surgical interventions. Percutaneous rhizotomy using stereotactic radiofrequency lesioning techniques appears to have at least equivalent results.

Microvascular Decompression

Microvascular decompression (MVD) is a nondestructive method that provides the highest likelihood of sustained pain relief from TN of any surgical procedure. The rate of initial relief is approximately 95% to 95%, and the incidence of delayed recurrence is about 22%. A retromastoid craniectomy is performed and microdissection techniques are employed to explore the root entry zone of the affected trigeminal nerve at the brainstem, and to move away any vascular structures that impinge on this region. In one series, arterial compression was identified in 70%, venous in 7%, and in 23% there was no recognized abnormality. A Teflon pledget is placed to cushion the nerve away from the mobilized vessel. Brainstem auditory evoked responses (BAERs) and facial nerve responses are monitored intraoperatively to minimize traction injuries of the eighth and seventh cranial nerves.

Barker et al reported on the experience of Peter Jannetta at the University of Pittsburgh in performance of 1204 MVD surgeries. At one year, 80% of patients were pain free and 8% had greater than 75% pain relief. At ten years, 70% remained pain free and 4% had greater than 75% pain relief. The mortality rate for this surgery is less than 1%. Morbidity includes transient or permanent facial dysesthesias in less than 5%, facial numbness in 1.65%, deafness in 1%, facial paresis in 0.9%, extraocular palsies in 0.15%, CSF leak in 1.5%, meningitis in 0.4%, Hydrocephalus in 0.15%, hematoma in 0.3%, and brainstem infarct in 0.07%.

The advantages of microvascular decompression are that it treats the primary etiology of the pain, the trigeminal nerve is preserved anatomically and functionally, postoperative pain relief does not require production of a new sensory deficit, the initial postoperative results are superior, and the rate of symptom recurrence is relatively low. Because of its nondestructive nature and its high success rate, MVD is typically recommended as the first line of surgical therapy for patients who are under the age of 70 and in otherwise good health.

Gamma Knife Radiosurgery

Leksell first targeted the Gasserian ganglion with radiosurgery for trigeminal neuralgia in 1951. Inconsistent results led Lindquist and Rand to conclude that the ganglion was not an optimal target. With the targeting of the trigeminal nerve adjacent to the pons, superior results have been achieved.

Gamma Knife stereotactic radiosurgery (GKS) has become a mainstay in the surgical treatment of selected cases of medically refractory TN. The neurosurgeon affixes a stereotactic frame to the patient’s head prior to MRI scanning for targeting purposes. Computer-assisted treatment planning allows the surgeon to target the root entry zone of the affected trigeminal nerve. A single isocenter employing a 4 millimeter collimator focuses 201 beams of cobalt radiation on this region, delivering about 60 to 90 gray in a single fraction. The rapid fall-off of dose at the edge of the treatment volume largely spares surrounding structures. GKS has the advantage of being relatively noninvasive and requiring no incisions. This enables the neurosurgical treatment of patients who are elderly, have significant medical conditions and risks, or take anticoagulant medications.

It is hypothesized that radiosurgery causes a blockade of ephaptic transmission through the trigeminal nerve. There is a latency of one month (range, one-day to three months) until therapeutic benefit can be expected to accrue. The initial rate of any improvement is 86% at six months, with sustained benefit seen in 55-75% of patients. Prior surgery does not significantly affect the results after radiosurgery. After complete relief, only 10% of patients relapse, usually within a year. With this regimen, 10% of patients experience slight facial numbness, with extremely rare reports of anhidrosis dolorosa, and no reported mortality.

In 1996, a multicenter study evaluated Gamma Knife radiosurgery targeting the proximal trigeminal nerve near the pons. The 4 millimeter isocenter was placed 2 to 4 millimeters anterior to the junction of the trigeminal nerve and the pons, so that the brainstem surface was irradiated at no more than the 30% isodose. Fifty patients were treated and followed for 18 months. Complete relief of pain was seen in 58%, significant improvement (50-90% relief) in 36%, and no benefit resulted in 6%. A treatment dose of 70 to 90 Gy was more likely to provide complete pain relief than a dose of 60 to 65 Gy. A randomized prospective dose escalation trial comparing 70 Gy versus 90 Gy demonstrated an increased incidence (32%) of bothersome dysesthesias with higher dose. A prospective randomized trial comparing treatment with one versus two isocenters demonstrated a higher incidence of paresthesias related to the greater length of nerve irradiated.

Massager et al retrospectively compared three treatment groups: Gamma Knife surgery to the retrostellar trigeminal nerve root with less than 90 Gy, with 90 Gy, or 90 Gy plus selective beam channel blocking. The portion of the trigeminal nerve targeted was anterior to the Ombeterer-Redlich zone, the pontine root entry zone that has been related to microvascular compression and was therefore selected as the target at the University of Pittsburgh and the Mayo Clinic. Beam channel blocking was employed to minimize dose to the motor corticospinal
pathways at the lateral anterior pons, with the consequence of increasing integral dose to the fifth nerve. Increasing integral dose to the trigeminal nerve in these three groups was associated with a decreased incidence of mild hypalgesia from 15% to 21% to 49%, and that of both severe hypalgesia from 14% to 2.4% to 10%. The percentages of pain-free outcomes were 66%, 77%, and 84%, greater than 90% pain reduction was seen in 81%, 85%, and 90%, respectively. There was a significant association between the effectiveness of GKS and development of side effects.

Patients with atypical trigeminal neuralgia or trigeminal neuralgia in the setting of multiple surgical procedures often experience recurrence of their pain. Postherpetic neuralgia treated with radiosurgery shows an initial 38% success rate after 6 to 13 months, with recurrence of pain in one-third of patients. Patients with facial pain due to intracranial tumors often derive relief of their pain after radiosurgery directed to the tumor, approximately 43% later experience recurrence of their pain.31,32,34,38

GKS provides a means for a good probability of therapeutic benefit and an extremely low risk of complications in patients unwilling or unable to undergo other surgical procedures for TN.35 Investigators using linear accelerator (UNAC) stereotactic radiosurgery systems have reported comparable results for treating TN, although with slightly lower success rates and slightly higher complication rates than GKS.36-38

Percutaneous Radiofrequency Rhizotomy

Kirscher performed electrocoagulation of the Gasserian ganglion in 1932.40 Complications due to uncontrolled heat spread limited acceptance of this procedure.41 Very soft retractor techniques to include short-acting anesthetic allowed that patient awakening during surgery for sensory testing, electrical stimulation for more precise localization in the ganglion, radiofrequency current for lesion production, and temperature monitoring for lesion control.42-44 Additional refinements by Tew and Taha and Nugent included the use of a curved radiofrequency needle to access individual nerve distributions.45 Letcher and Goldberg demonstrated that the A-beta and C (nociceptive) fibers had their compound action potentials blocked at lower temperatures than those of the larger A-alpha and A-beta (tactile) fibers, suggesting a mechanism of action for rhizotomy.46

Radiofrequency rhizotomy (RFR) is a widely used technique that carries low risk to the patient, and can be repeated if necessary.46 In this surgical procedure, a curved radiofrequency thermo-coagulation needle is inserted percutaneously from the cheek into the Gasserian ganglion via the foramen ovale under fluoroscopic guidance. Three anatomic landmarks were described by Hartel: a point 3 centimeters anterior to the external auditory meatus, the medial aspect of the ear, and a point 5 centimeters lateral to the orbit.47 A 100 millimeter 20 gauge stylet with cannula is inserted toward a point 3 centimeters anterior to the external auditory meatus, the medial aspect

... continuation of radiographic sequelae from the trigeminal cistern alone was sufficient to produce relief of neuralgia. The glycerol was employed to carry tantamount in order to target the Gasserian ganglion with Gamma Knife radiosurgery.48

Percutaneous Glycerol Rhizotomy

Therapeutic injections into the trigeminal cistern have been documented since 1910. Harris achieved pain relief with alcohol at the cost of anesthesia and the risk of multiple cranial neuropathies. In 1981, Hakanson described that injection of glycerol into the trigeminal cistern alone was sufficient to produce relief of neuralgia. The glycerol had been employed to carry tantamount in order to target the Gasserian ganglion with Gamma Knife radiosurgery.49

Percutaneous retrogasserian glycerol rhizotomy (PRGR) provides initial pain relief in 90% of patients. The onset of pain relief is between 24 hours and two weeks.50 In a series of 365 patients, Lunsford reported that long-term pain relief ranges from 45-90%. The average duration of pain relief is less than three years. Approximately 45% of patients require continuation of at least some of their preoperatively prescribed medications. After 11 years, 71% of 365 patients underwent only one, while 23% needed two, 5% needed three, and 1% required four glycerol rhizotomies to maintain pain relief. Of these 365 patients, 77% experienced relief of pain, with 55% off all medications.51,52

Persistant facial sensory loss is reported as significantly less than that seen with radiofrequency rhizotomy. After PRGR, 50% of patients experience some sensory loss: mild in 32%, moderate in 13%, and dense in 6%. Corneal sensory loss was seen in 4% of patients, and anesthesia dolorosa in 0.1-8%.53,54

Teflon pledget maintains microvascular decompression.
Trigeminal Neurorcoma

Peripheral destructive procedures for trigeminal neuroroma were described by Schlichting in 1748, and Marechal and Andre in 1732. Supraorbital, infraorbital angular, and superior maxillary nerves have been affected by neuroroma in patients who have failed other surgeries or who are elderly or medically unable to undergo another procedure. Superficial and infraorbital neurorcoma typically are avoided by using V1 with or without V2 numbness. Neurorcoma is relatively easy to perform and is associated with a low incidence of morbidity or mortality. Pain relief in the distribution of the profound anesthesia is typical, with an average duration of three months.

Stereotactic Surgery, Trigeminal Nerve Stimulation and Motor Cortex Stimulation for Chronic Facial Pain

Stereotactically directed lesioning procedures treating refractory facial pain have targetted the trigeminal nucleus caudalis, the trigeminal, the anterior limb of the internal capsule, and the cingulate gyrus. Deep brain stimulation of the periaqueductal gray and periventricular regions has been advocated for chronic pain; however, pain relief in the distribution of the profound anesthesia is typical for 86% of patients (40/47 patients) with post-dental surgery chronic pain, 92% (11/12 patients) at surgery might be considered candidates for selective trigeminal sectioning.

Ideally, the best chance of combining low risk and high therapeutic yield is afforded at the time of selecting the first surgical procedure for the patient. The risk of anesthesia dolorosa increases with a greater degree of numbness from any destructive procedure, and increases after undergoing multiple destructive procedures. At present, the currently available best surgical technique appears to be one that offers the best chance of combining low risk and high therapeutic yield.

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Trigeminal Neuroroma

First and foremost, the diagnosis of TN must be carefully and definitively established. The initial treatment of TN is typically noninvasive surgery, and a reasonable alternative to surgical resection. The relatively noninvasive surgery is well tolerated, has a reasonable success rate and has a low incidence of permanent facial numbness or anesthesia dolorosa. Patients who have more immediate relief from pain than that afforded by GKS, but who are not candidates for MVD, should be offered the option of RFR, PRGR, or PBC.

Patients whose pain recurs after successful MVD may be offered the alternatives of GKS, RFR, PRGR or PBC.

Patients whose pain recurs after an initially successful GKS may be offered a second GKS or the alternatives of RFR, PRGR, PBC, selective trigeminal sectioning, or percutaneous retrogasserian glycerol injection.

Patients whose pain recurs after a second GKS, or those who failed to secure initial benefit after a GKS, may be offered RFR, PRGR, or PBC, selective trigeminal sectioning, or percutaneous retrogasserian glycerol injection.

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Memory is seen as a key function in mental status assessments. It may be evaluated on a formal basis through structured mental status testing, or informally through clinician assessment of the quality of answers in routine conversation and the collection of core data about the individual. Memory disorders may be transient, such as after a seizure or mild head injury, or profound, such as in Alzheimer's disease or Korsakoff's syndrome. This review will cover the anatomy and forms of memory, and clinical assessment of primary amnestic disorders.

Anatomy

The locus of memory has been debated since time immemorial. Even through much of the 20th century, animal experiments by Karl Lashley and others seemed to indicate a cortical localization but no distinct "memory center." However, evidence from several sources have shown that specific structures appear key to this distributed system.

The importance of the medial temporal lobe memory system has been advanced particularly through the study of unique patients, including an individual known in the literature as H.M.1,2 This man underwent a bilateral temporal lobectomy in the 1950s and subsequently has had a severe anterograde amnesia with virtual loss of words seen in anomic aphasia could also be construed as an inability of word retrieval, hence a form of amnesia. Apraxia, seen in association with left hemispheric lesions, can be seen as a disorder of procedural memory.

In order to align with current neuroanatomical concepts, it is useful to strive for a common language, adopting the framework developed by neuropsychologists who have studied this subject in greatest detail. Distinctions are made between short-term and long-term memory, motor memory and memory for words, colors, events and how to do complex skills. There is retrograde and anterograde amnesia, such as in head trauma and Korsakoff's syndrome,1 the severity of which correlates with trauma dose. Memories may be consciously encoded (explicit memory) and consciously recalled (declarative), or implicit and nondeclarative.

Most agree that there are four primary types of memory: 4

- Episodic
- Semantic
- Procedural
- Working

Episodic memory involves the temporal lobes, anterior thalamic nuclei, prefrontal cortex, fornix and mammillary bodies.1,4 Examples would include recalling recent events, a brief story, or where the patient went to dinner last week. Memories may be stored for minutes up to years. In general, shorter-term episodic memories are more vulnerable to brain injuries and disorders.

Semantic memory is a long-term storage modality whose anatomic substrate includes the inferolateral temporal lobes. Examples include recalling who was the first president, the color of an apple and the meaning of different words. This too is a long-term storage modality.

Procedural memory relies on components of the motor system such as basal ganglia, cerebellum and supplementary motor areas. The classic example is captured in the saying, "You never forget how to ride a bicycle."

Working memory is a short-term system which has phonological components involving language areas (Broca's and Wernicke's areas) and spatial memories involving prefrontal cortex and visual associative areas. Examples would include recalling something one just heard (e.g. a bird song) or mentally recalling where something was in relation to other objects.

Terminology

Perhaps no aspect of memory perplexes more than the terminology; the vernacular language of neurologists and neurosurgeons also contributes to the confusion. The frequent lack of operational definitions and the ambiguity and lack of subtlety in our language also contributes to these difficulties. For example, the loss of words seen in amnestic aphasia could also be construed as an inability of word retrieval, hence a form of amnesia. Apraxia, seen in association with left hemispheric lesions, can be seen as a disorder of procedural memory.

Assessment of Memory

Memory assessment begins with casual conversation undertaken at the start of a clinical encounter. The clinician may note that the patient "looks for validation" or hesitates even when recalling common information such as the number of children he or she has or where he or she lives. As a practical matter, it is useful to restrict testing to items where the examiner knows the answer or has the answer readily available, so that confabulation can be minimized.

Relevant items in the patient's history include the mode of onset and precipitating events, comorbid illnesses and family history. Patients may use terms such as fogginess or confusion, and refer to getting lost or misplacing items. They may complain of non-recognition of friends or family members or lack of recall of names, especially of people they have known for long periods of time, etc. Informants often report repeated questioning, difficulty recalling appointments and difficulties with financial affairs. Although repeated questioning could be due to hearing loss, selective attention or receptive aphasia, repetitive questioning is one of the commonest symptoms reported in Alzheimer's disease (AD), the most common degenerative dementia.
Alzheimer's Disease

AD is the most common cause of dementia and is generally diagnosed in individuals presenting with progressive memory loss with loss in other cognitive domains, compromise of activities of daily living or social or occupational function and no other definable cause for their syndrome.

While the cause of AD is unknown, most authorities feel that beta-amyloid is the neurotoxic moiety in AD, and multiple lines of evidence support this hypothesis. Other theories of AD pathogenesis include the tau hypothesis, disturbances in cell-cycle regulation, a brain-inflammation hypothesis and several other mechanisms. However, it is recognized that neuropathological indices correlate poorly with clinical symptoms, and that the cause or causes of AD are extremely complex.

There are three known genetic mechanisms for early onset AD (mutations in the amyloid precursor protein, presenilin-1 and presenilin-2), all involved with increased production of beta-amyloid. Individuals with trisomy 21 all develop cerebral amyloidosis and clinical AD. This is thought to be related to a gene dose effect of the amyloid precursor protein located on chromosome 21. Individuals with one or more apolipoprotein E (APOE) ε4 alleles are at greater risk of developing AD, but it is not by any means certain that individuals with this allele will develop AD.

To avoid the risk of oversimplification, multiple other hypotheses and biochemical pathways and environmental effects appear to affect AD risk, such that AD can also be viewed as a complex disease trait with multiple determinants similar to atherosclerosis, diabetes mellitus or schizophrenia.

Memory in Alzheimer’s Disease

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Mild Cognitive Impairment and Dementia

With the increasing emphasis on “cognitive wellness,” clinicians are evaluating individuals who may be normal but have a family history of dementia that increases their risk, or who have only occasional memory problems of uncertain significance. Controversy exists about how best to assess such individuals. Comparisons with population norms for age, education and gender are straightforward, but variability in cognitive abilities suggests that false negative evaluations can be an issue. Intra-individual evaluation is more sensitive, but the starting “baseline” may need to be estimated based on educational and occupational achievement or other measures of premorbid intelligence.

Mild cognitive impairment (MCI) refers to individuals with objective memory dysfunction, usually >1.5 standard deviations below normal on one or more neuropsychological tests, but without functional compromise. This may occur in an isolated amnestic form, but multidomain and nonamnestic forms of MCI have been recognized. As formulated by Petersen and colleagues, MCI progression rates to Alzheimer’s disease average about 15% per year. Other authors have suggested that since a vast majority of individuals with MCI eventually progress to AD, it should be recognized as such. However, issues such as clinical and pathological heterogeneity and other forms of MCI, such as vascular MCI, have precluded consensus on these issues.

Despite the recognition that MCI often progresses to AD, a randomized trial of donepezil vs. vitamin E vs. placebo showed little benefit either in terms of lowering progression rates or definable cognitive outcomes.

Alzheimer’s Disease

AD is the most common cause of dementia and is generally diagnosed in individuals presenting with progressive memory loss with loss in other cognitive domains, compromise of activities of daily living or social or occupational function and no other definable cause for their syndrome.

While the cause of AD is unknown, most authorities feel that beta-amyloid is the neurotoxic moiety in AD, and multiple lines of evidence support this hypothesis. Other theories of AD pathogenesis include the tau hypothesis, disturbances in cell-cycle regulation, a brain-inflammation hypothesis and several other mechanisms. However, it is recognized that neuropathological indices correlate poorly with clinical symptoms, and that the cause or causes of AD are extremely complex.

There are three known genetic mechanisms for early onset AD (mutations in the amyloid precursor protein, presenilin-1 and presenilin-2), all involved with increased production of beta-amyloid. Individuals with trisomy 21 all develop cerebral amyloidosis and clinical AD. This is thought to be related to a gene dose effect of the amyloid precursor protein located on chromosome 21. Individuals with one or more apolipoprotein E (APOE) ε4 alleles are at greater risk of developing AD, but it is not by any means certain that individuals with this allele will develop AD.

To avoid the risk of oversimplification, multiple other hypotheses and biochemical pathways and environmental effects appear to affect AD risk, such that AD can also be viewed as a complex disease trait with multiple determinants similar to atherosclerosis, diabetes mellitus or schizophrenia.
Adult Epilepsy: A Review

By Mary Ann Werz, M.D., Ph.D.

Epilepsy is often incorrectly presumed to be a single disease. In reality, epilepsy is the tendency of the brain to produce unprovoked epileptic seizures, and many conditions can lead to this. The two major categories of epileptic seizures are generalized, with both hemispheres involved at seizure onset, or partial with a focal seizure onset.

Mesial Temporal Sclerosis
The pathology identified from tissue taken during en bloc temporal lobe resection for epilepsy has revealed mesial temporal sclerosis (MTS) as the sole pathology in about 65% of adult cases. MTS is defined as gliosis and loss of neurons within the hippocampal formation, especially hippocampal CA1 and CA3, and hilus of the dentate. MRI findings of MTS include decreased volume associated with increased fluid attenuated inversion recovery (FLAIR) and T2 signal of the hippocampal formation. These changes can be subtle even with the specialized imaging sequences and higher tesla field strength found at epilepsy centers. Epilepsy surgery is highly successful when MTS is the underlying pathology, with about 90% of patients remaining seizure-free at one year, and recent long-term studies showing about 80% seizure-free at 10 years. The pathophysiology of MTS is complex, and includes an association with complex febrile seizures in childhood. Complex febrile seizure means prolonged or lateralized clinical features of the seizures. For years, the causality of MTS and complex febrile seizures has been debated. Does MTS cause complex febrile seizures, or do complex febrile seizures cause MTS? Potential genetic and infectious contributions to the development of MTS have been identified. MTS may also develop in adults after trauma or status epilepticus. The severity of MTS may worsen with continued seizures. Close to 30% of patients with MTS have a history of febrile seizures that remit until adolescence or adulthood when nonfebrile focal seizures re-emerge and usually become intractable to medications. Data from epilepsy centers reveal that only 10-30% of patients with MTS on MRI can be controlled long-term with AEDs.

Abnormalities Categorized
In imaging negative temporal lobe epilepsy that has gone to en bloc temporal lobe resection, pathology often shows “microscopic” abnormalities deviating from the normal six-layer cortical structure. A panel of neurologists and neuropathologists in 2004 described and categorized these abnormalities. Abnormalities were categorized as Type 1 based on the lack of dysmorphic neurons and Type 2 based on the presence of such neurons. Type 1A includes architectural abnormalities of laminar or columnar organization such as cell clustering in layer 1 or tangential rather than perpendicular dendrites. Type 1B includes these architectural abnormalities and also giant or immature neurons. Type 2A shows dysmorphic neurons but no balloon cells, and Type 2B includes balloon cells. Balloon cells were first described by Taylor in 1971 and have an eosinophilic cytoplasm with large eccentric nuclei with immunohistochemical staining showing characteristics of both neurons and glia. Additionally, two types of tumors may be classified as “extreme” focal cortical dysplasia: dysmyelopathic neuronal tumors (DNT) and gangliogliomas. Type 1 focal cortical dysplasia can be found in 1.7% of nonepilepsy cases at autopsy and may be associated with cognitive impairment rather than epilepsy.

Electrocorticography has suggested a relatively specific firing pattern within areas of microdysgenesis. The appearance of microdysgenesis on neuroimaging may be very subtle and includes cortical thickening, blurring of gray-white matter junction, and underlying white matter abnormalities that include a “funnel” from cortex to the ventricle that presumably follows the migration pathway of neurons.
Microdysgenesis in the temporal lobe is typically only of Type 1A (52/56 cases reported by Widdess-Walsh et al). Other types of cortical dysplasia (Type 1B and Type 2) are typically frontal or multilobar. Seizure onset in patients with cortical dysgenesis is usually during childhood but seizure onset occasionally is as late as the fourth decade. Most patients have better than low average intellect (full-scale IQ>80) and may even be highly functioning (FSIQ 120). Risk factors were rare except for febrile seizures. Surgical outcome for temporal lobectomies with pathology showing dysplasia has ranged from 60-70% free of disabling seizures ( Engel Class I) with a mean followup duration of 2.8 to 4.4 years. This outcome result is less positive than that reported for isolated MTS (80% free of disabling seizures at 10 years). The presumption is that microdysgenesis is more diffuse and less circumscribed than MTS. Overall seizure-free rates for all epilepsy surgical cases demonstrating cortical dysplasia, including extratemporal resection, is only 30-65%.3, 4

Cortical Dysplasia in Epilepsy

The incidence of cortical dysplasia in epilepsy surgical series has ranged from 12-40%.6, 7 In our case series of 55 adult epilepsy surgeries at University Hospitals Case Medical Center, 42% have had focal cortical dysplasia with Type 1 in 15%, Type 2 in 11%, and “extreme” focal dysplasia (DNT/ganglioglioma) in 17%. The rate of focal cortical dysplasia is far higher in pediatric epilepsy surgical series with an incidence of 80% reported in children under the age of 3.8 Cortical dysgenesis is presumed to involve abnormal cell differentiation, abnormal cell migration and abnormal programmed cell death. The precise timing of the origin of cortical dysplasia during development as well as the genetic and environmental factors causing focal cortical dysplasia need to be elucidated. The ultimate goal would be prevention, though medical or surgical options for improved treatment are likely to come first. Surgical therapy would be aided by more advanced neuroimaging and physiological modalities allowing better identification of the anatomical extent of cortical dysplasia as well as the area necessary for seizure generation (the epileptogenic zone).

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REFERENCES

Intraoperative photograph after resection of epileptogenic frontotemporal cortical dysplasia.

By Deborah Blades, M.D.

More than 200,000 lumbar laminotomies with discectomy are performed each year in the United States to treat lumbar disc herniation. In the literature, recurrence rates are reported as ranging from 3-22%. This translates to approximately 20,000 patients undergoing further surgery to address recurrent disc herniations each year.

Unfortunately, there is no consensus about how best to address these patients mainly because the reasons for recurrence vary. Some authors believe that repeat laminotomy and discectomy alone is the treatment of choice, whereas others believe fusion (posterolateral with pedicular fixation, posterior lumbar interbody) should accompany the laminectomy and discectomy. A survey was sent to members of the North American Spine Society presenting the case of a 35-year-old active female, six months following an L4-5 lumbar microdiscectomy who had recurrent leg pain due to reherniation of disc material. Of the respondents, 57% chose repeat discectomy without fusion while 43% chose discectomy with fusion. It is clear that individual factors require evaluation prior to making definitive surgical decisions.

The literature is replete with information regarding failed back syndrome as it relates to the multiply operated patient. However, two seminal series specifically address the issue of the treatment of recurrent disc herniation. Epstein et al reported on 47 patients with recurrent disc herniation treated by discectomy without fusion. The followup period ranged from one to five years in 37 patients and five to 10 years in 10 patients. Among these patients, 81% had good results, 13% fair and 6% poor. Four patients underwent a third operation in their series. Connolly also reported results following recurrent disc herniation in 182 patients. Nineteen (10%) were treated for recurrence during 7.6 years without enlisting a fusion procedure; 74% had good results in that series. Subsequent reports indicate fairly similar results.

It is also important to note that outcome is unaffected by the level at which disc herniation occurs. Gender may play a role, in that reherniation appears to occur at a higher frequency in men than women. The risk of reherniation is certainly ever-present, but it appears that the major risk of herniation occurs in the first one to three years after surgery. Certainly, higher rates of recurrent disc herniation would be noted with longer followup and longer periods of observation.

The literature suggests that fusion is rarely required after discectomy. Cauchoxi et al reported that 520 patients treated with discectomy, only nine (1.7%) required fusion one to 20 years after initial discectomy. Thirty-eight (6.6%) patients in this series were treated for recurrent disc herniation. Gill and Freamoyer identified instability after discectomy as the cause for 18% of overall surgical failures.
The term “recurrence” in this patient population suggests that there has been a period of six to 12 months of true leg pain relief. Waddell et al. and Finnegan et al. have noted that a period of less than six months relief from a previous operation predicted a poorer prognosis for subsequent reoperation.

The keys to diagnosis in patients with recurrent lumbar disc herniation are a clear history, full examination and an appropriate radiographic study to discern scar from recurrent disc material. Magnetic resonance imaging evaluation without and with gadolinium is essential to determine the cause of recurrent leg pain in the previously operated patient. Certainly, once diagnosis of recurrent disc herniation is made, nonoperative measures can be enlisted as long as the patient is neurologically intact and continent of bowel and bladder. If no symptomatic improvement is noted, then surgical intervention in the form of repeat discectomy can be done without fusion. If instability has been identified, then fusion would be performed at the same setting.

There is no doubt that recurrent disc herniation is a risk in patients undergoing discectomy. Data would suggest that patients do well overall with reoperation as long as a correlation exists between the neurologic examination and the level of disc herniation. In the absence of clear signs of instability, discectomy alone is sufficient in the treatment of this patient population.

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The mean onset of symptoms is about 5 years of age, and greatest tic severity occurs around 10 years. Tic frequency and severity wax and wane with time, and are reported to diminish by age 18. However, about half of all affected individuals continue to experience tic symptoms in adulthood. Prevalence in children is estimated to be as high as 1-2%. Therefore, Tourette syndrome in adults is not insubstantial. Tics can be demonstrated in adults even when not self-reported. Over one quarter of an adult sample was disabled.

Anatomic, Physiologic and Pharmacologic Substrate of TS

The etiopathology of TS is not yet clear. Genetic transmission is well documented. A recent association with the SLTRK1 gene has been reported. Some investigators have emphasized a possible role of infections and immune response in the development of TS and other pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS), but this is not likely to be a major factor in most patients with TS.

The anatomic and physiologic substrate has long been believed to involve the basal ganglia and the cortico-striato-pallido-thalamo-cortical (CSTC) loop. By the late 1970s, it was apparent that antiparkinsonian agents could suppress tics. The basal ganglia are a major target of the dopaminergic system projecting from the brainstem. Pathologic studies, anatomic imaging studies using magnetic resonance imaging, and functional neuroimaging studies using functional MRI, positron emission tomography and single photon emission computed tomography have revealed various abnormalities of basal ganglia and frontal cortex.

Models of basal ganglia interactions and function have been evolving to attempt to explain basal ganglia dysfunction in a variety of neurological diseases including Parkinsonism, chorea, dystonia and TS. The basal ganglia are the target of a large set of
parallel pathways arising from all parts of the cerebral cortex, and the output pathways remain essentially segregated in channels through the thalamus and back to the cerebral cortex.12,13 Our understanding has expanded to include more appreciation of specific interconnections between basal ganglia and midline thalamic nuclei.

In current concepts of normal basal ganglia function, the system is optimized to select desired movement programs and suppress competing or unwanted movements.12,13 In hyperkinetic movement disorders, elements of motor programs are inappropriately selected. Because the system contains not only motor but also prefrontal and limbic pathways serving cognitive and emotional functions, dysfunction of the basal ganglia commonly results in behavioral and affective disturbances. Within the striatal circuitry, abnormalities in the interaction among these systems may lead to inappropriate expression of specific tic behaviors14,15 and may explain the high incidence of obsessive-compulsive symptoms (OCS) and behaviors (OCD). Certain aspects of OCS/OCD in TS are sufficiently distinct from those of OCD10 to suggest separate pathophysiological origins.

Medical and Behavioral Treatment of TS
Pharmacologic treatment for Tourette syndrome has focused on dopamine receptor blockers (haloperidol, pimozide, fluphenazine and other typical neuroleptics), presynaptic catadolinamide depletors (reserpine, tetrabenazine), or central alpha-2 adrenergic receptor blockade (clonidine).14 Tics are rarely eradicated entirely, the goal of medication is to achieve maximum control with minimal side effects. About 13-22% of adult individuals with Tourette syndrome must continue to take medications for tics. Some adult patients remain symptomatic with clinically disabling tics despite maximal medical therapy. Several specific behavioral techniques, as well as alternative treatments, have been investigated. However, these methods are incompletely studied or of limited efficacy.11 Some individuals benefit from local injections of botulinum toxin, but this strategy can be applied only to a very limited distribution of tics. For medically refractory individuals, there is no satisfactory alternative to symptom control. It is in these cases that consideration is given to the patient’s candidacy for palliative surgical therapy.

Surgical Treatment of TS
Historically, a variety of neurosurgical lesioning procedures have been employed in an effort to palliate the symptoms of patients with severe, medically refractory TS. Many deep brain targets have been explored in the frontal lobes, the cingulate gyrus, the anterior limb of the internal capsule, the limbic system, and subthalamic zona interna.14 Some success has been achieved with amelioration of psychiatric aspects of TS when these are present, especially those involving manifestations of OCD. On the other hand, control of the motor and vocal tics has been more variable and less significant. Risk of adverse effects related to these lesioning procedures has been high.

Other surgeons have stereotactically targeted the thalamus and basal ganglia for therapeutic lesioning, with more beneficial results. Cooper (1969)16 reported on six patients with severe motor tics who received significant benefit from staged bilateral ventrolateral (VL) thalamotomies. Hassler and Dieckmann (1982)17 reported on 15 patients with excellent, durable clinical results after undergoing bilateral thermoablation of the rostral intralaminar nuclei and medial thalamic nuclei. de Divitiis et al (1977)18 reported on three patients who underwent unilateral right-sided radiofrequency lesioning of the dorsal medial and intralaminar nuclei; two achieved complete remission and one had a minimal reduction in tics. Korzen et al (1991)19 reported on one patient who experienced an excellent, sustained benefit after bilateral VL thalamotomies.

In other movement disorders (such as Parkinson’s disease, essential tremor or dystonia), stereotactic lesioning procedures have largely been replaced by stereotactic implantation of deep brain stimulation electrodes (DBS). DBS has been shown to have a higher incidence of therapeutic success and a lower incidence of surgical complications than do lesioning procedures. In DBS, indwelling electrodes are positioned in specific targets in deep forebrain structures, and a continuous electrical high frequency square wave train is provided by a pulse generator implanted in the chest wall. DBS is considered safer and far less destructive than lesioning procedures, and therefore potentially reversible in cases of mistargeting, adverse effects or future therapeutic developments.

Deep Brain Stimulation for TS
Limited data are available regarding the efficacy of DBS in Tourette syndrome. A case series of three patients was reported,16 targeting the ventral thalamus bilaterally, the first of these cases had been reported by Vandervoelle et al (1999).19 These authors carefully considered the existing lesion-based reports and determined that the targets of Hassler and Dieckmann were most likely to result in tic reduction. The electrode trajectory was chosen to allow for the four contact points along the stimulating electrode to be positioned at or near the lesioning sites within the thalamus.12 In this case series, tic frequency was determined to have been reduced by 70-90% with the stimulator on as compared to the stimulator-off state.

University Hospitals Experience
At University Hospitals Case Medical Center, after appropriate informed consent had been obtained, we performed a sentinel DBS implantation in 2004 targeting thalamic regions reported by Hassler (1982)20 and Visser-Vandewalle et al (2003)21 in a 30-year-old individual who had Tourette syndrome since before the age of 5. Tic frequency and severity was reduced dramatically, as measured by a video scoring scale.12 The individual continues to enjoy minimal symptomatology from tics three years after initial activation of his stimulators.

Based on the information available in 2005, our group conducted a pilot trial of thalamic DBS in five individuals.22 Stimulators were activated unilaterally or bilaterally in a double-blind fashion, with each subject serving as his own control. A statistically significant reduction of tic frequency and severity was identified; three of five patients clearly benefited by three months followup. At the one-year followup, four of five reported improved tic symptoms and quality of life.23
Target Options for DBS in TS

Since we began our pilot trial, a few other cases, case series, open-label trials, and small double-blind studies have been reported. Some authors have targeted the thalamus, while others have approached the globus pallidus pars interna (GPi).

A total of 30 subjects with thalamic stimulation have been reported in articles or in abstract form. These include three by Visser-Vandewalle et al (2003),18 one by van der Linden et al (2002),23 one by Houeto et al (2003),25 one by Ackermann et al (2006),26 six by our group,27,28 and eighteen by Porta et al (2006).29 Reported outcomes usually have been expressed in terms of tic frequencies (usually video-based) or a widely used rating scale, the Yale Global Tic Severity Scale (YGTTSS).27 Followup periods have ranged from a few months to more than five years. In successful cases, reduction of tic frequency has been in the 70%-100% range.

The precise thalamic target is not yet established. The anchor point for the electrode (tip contact) is commonly reported to be intralaminar, in the centromedian-parafascicular (CM-PM) nuclear complex.30 This is given with respect to the midcommissural point as 5mm lateral, 4mm posterior, and 0mm inferior.19 However, as there are four electrodes to choose from to cover a span of 10.5mm along the trajectory (given a set of target coordinates and angles in sagittal and coronal planes) and therefore possible sites of effective stimulation. It remains unanswered whether the optimum target is intralaminar or more lateral, dorsal and anterior.

Stimulation of the GPi has been reported in four patients,21,25,29,31 as well as in a double-blind trial.32 Most thalamic stimulation, outcome measures have included tic frequencies, YGTTSS and other indices. Results have been comparable to those of thalamic stimulation.

Most authors state that their GPi target is that used for other movement disorders such as PD or dystonia. One group (Houeto et al 2005)33 explicitly targeted “limbic pallidum.” This approach and target are sufficiently distinct (given a set of target coordinates and angles in sagittal and coronal planes) and therefore possible sites of effective stimulation. It remains unanswered whether the optimum target is intralaminar or more lateral, dorsal and anterior.

Successful stimulation in the thalamus and GPi is consistent with an understanding of TS as a hyperkinetic movement disorder involving dysfunction of cortico-striato-pallido-thalamo-cortical loops. Loss of apparent was in a single case report of implantation of bilateral DBS electrode tips in the nucleus accumbens and contacts along the anterior limit of the internal capsule. TIC reduction in this 37-year-old woman with self-injurious tic behavior, but no psychiatric history, was modest, about 20% or so,24 though the self-injurious behavior was significantly reduced. Profound effects on mood were described with electrodes in these locations. The nucleus accumbens is part of the “limbic” basal ganglia and is likely to be more involved with emotional states than with movement per se. The nucleus accumbens and anterior limit of internal capsule have been proposed as targets for treatment of OCD.21 Although OCD is linked with TS, the available evidence suggests that TS is not a subset of OCD. Predictably, targeting of structures thought to be involved in obsessive-compulsive symptoms and behavior might not have as potent a direct effect on tic reduction as a target more embedded in the motor loops. A modest effect, related to influence on fibers in passage, is plausible.

Prospective Surgical Trial

Sufficient data exist to suggest that DBS is worth exploring as a possible efficacious treatment for medically refractory TS. However, most data are derived from case reports, case series, open-label trials, “in ot” studies and our own pilot double-blind randomized controlled trial of five subjects.23 As can be appreciated from the foregoing discussion, many questions remain unanswered.

Preliminary analysis of our pilot study data suggests a significant reduction in deep brain stimulation in patients with medically refractory Tourette syndrome. In our judgment, we would not anticipate widespread acceptance of this procedure for TS without data obtained in more subjects. Therefore a definitive trial is needed. We are preparing to conduct a definitive prospective randomized double-blind controlled surgical trial at University Hospitals Case Medical Center, based on our experience with the pilot trial and the current evidence from published series. The surgical approach and the motor outcomes presented here are consistent with recently published standards for design and conduct of a trial of DBS.
Target Audience
This continuing medical education (CME) program is intended for all physicians, particularly family practice and internal medicine physicians, neurologists and neurological surgeons interested in the latest advances in the management of neurological disorders.

Educational Objectives
Upon completion of this educational activity, the participant should be able to:

- Understand the management of adult epilepsy patients.
- Recognize the management choices for patients with recurrent lumbar disc herniation.
- Understand the use of deep brain stimulation in the management of patients with Tourette syndrome.
- Review the management of patients with memory dysfunction.
- Be aware of tumor vaccines for malignant gliomas.
- Understand management of patients with trigeminal neuralgia.

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