



Neurological Institute Journal

- Vaccines for Brain Tumors
- Trigeminal Neuralgia: Innovative Treatments
- Evaluating Memory Dysfunction
- Adult Epilepsy
- Recurrent Lumbar Disc Herniation
- Deep Brain Stimulation for Tourette Syndrome



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Volume 1 • Number 1 • Winter 2008

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 regarding advances in the basic sciences and clinical care of patients with neurological disorders. As a sign of

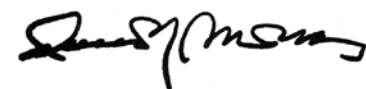
our commitment to education, research and clinical care, we have provided an opportunity for you to assess yourselves after reading each article and to simultaneously receive appropriate credits for your Continuing Medical Education.

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 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 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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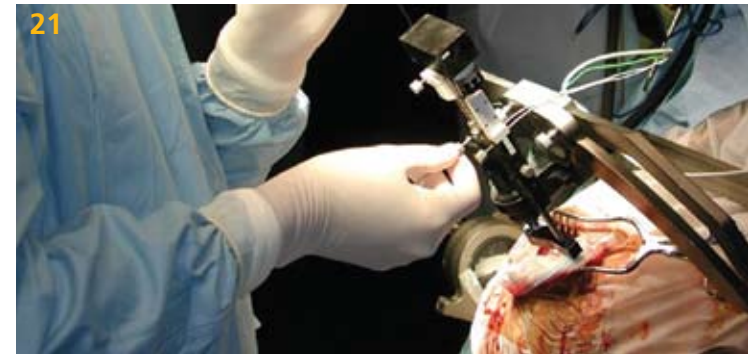
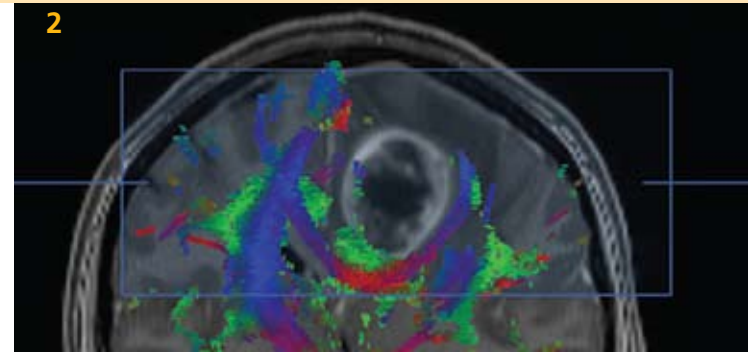
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Editorial board members, with the exception of Dr. Riley, report no financial relationships related to articles appearing in this issue of the Neurological Institute Journal. See page 25 for Dr. Riley's disclosure statement.

TABLE OF CONTENTS

- 2 Immunotherapy for Brain Tumors: New Hope with Minimal Toxicity**
Andrew E. Sloan, M.D., FACS
- 5 Trigeminal Neuralgia: Innovative Treatment Options Abound**
Robert J. Maciunas, M.D., MPH, FACS
- 12 Evaluation of Memory Dysfunction**
Alan J. Lerner, M.D.
- 16 Adult Epilepsy: A Review**
Mary Ann Werz, M.D., Ph.D.
- 19 Recurrent Lumbar Disc Herniation: Assessment of Management Choices**
Deborah Blades, M.D.
- 21 Deep Brain Stimulation for Tourette Syndrome**
Brian N. Maddux, M.D., Ph.D.
Mike R. Schoenberg, Ph.D., ABPP-CN
Christina Whitney, RNCS, DNSc
David E. Riley, M.D.
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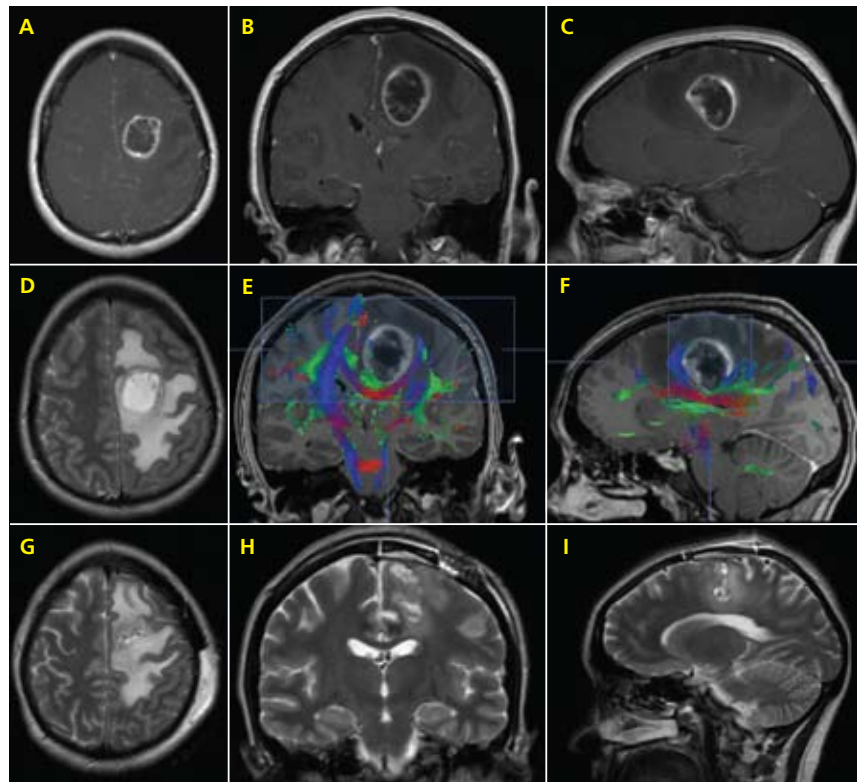
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Immunotherapy for Brain Tumors: New Hope with Minimal Toxicity



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). T2-weighted axial image (D) and diffusion tensor imaging (DTI) show marked edema in entire left hemisphere with tumor shifting primary motor tracts inferiorly (green) and anteriorly (blue) (E, F). Image-guided surgical techniques coupled with DTI enable the surgeon to precisely identify both tumor and distorted normal anatomy to accomplish image complete resection of tumor with decreased edema, while preserving normal anatomical pathways (G, H, I). The patient's strength actually improved postoperatively.

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 18,600 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

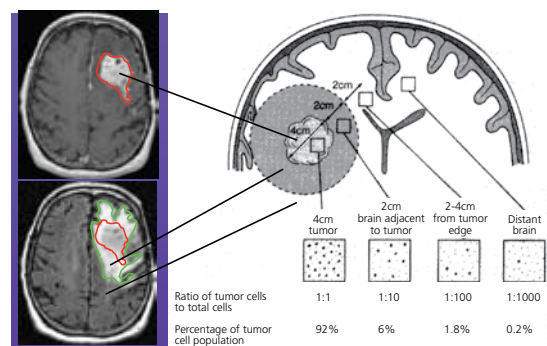


Figure 1 – In patients with glioma, microscopic glioma typically infiltrates deep into the brain far outside the border of the enhancing portion of the tumor seen on MRI. (Illustration courtesy of Dr. Christoph Pedain, BrainLAB.)

tumor diffusely infiltrating the brain prior to diagnosis (Figure 1). “Local control” can be achieved by surgery and radiation 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 glioma 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 immunosurveillance (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 her/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 one 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

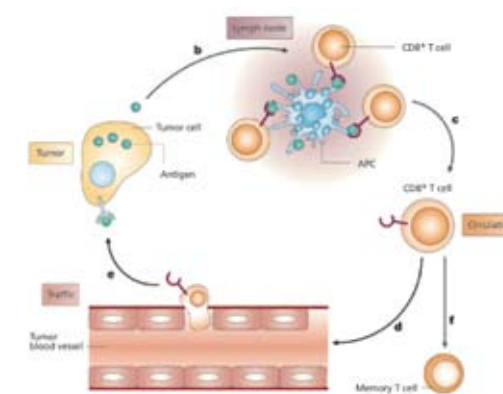


Figure 2 – The process of immunosurveillance begins when T-lymphocytes encounter tumor cells after leaving the blood vessels. T-lymphocytes then travel to lymph nodes where they encounter antigen-presenting cells, usually dendritic cells, and stimulate CD8 cytolytic T-cells (CTLs). The CTLs then return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

BRAIN TUMOR CENTER

Robert J. Maciunas, M.D., Director

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.



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likely. DC-based immunotherapy is typically more complex than peptide vaccines in that the protocols usually require leukopheresis to produce DCs as well as fresh autologous tumor to prepare the vaccine. Because the tumor antigens are usually unknown, immunological monitoring is usually not feasible, which makes it more difficult to know if the immune system has been adequately activated.

Lastly, adoptive immunotherapy typically begins with an active immunotherapy phase followed by in vitro expansion of cellular products, which are then reinfused into the patient. Preliminary studies have also demonstrated the efficacy of adoptive immunotherapy for glioma (Figure 4).³

New Trials at UH Neurological Institute

Two new trials being conducted at the Neurological Institute and Ireland Cancer Center of University Hospitals Case Medical Center combine standard radiation and chemotherapy with tumor vaccines for the treatment of newly diagnosed GBM.

The Celldex Trial utilizes CDX-110, a peptide vaccine comprised of the extracellular portion of the epidermal growth factor receptor known as EGFRviii conjugated with a carrier protein known as KLH. This mutation is not found in normal brain, but is found in 40-60% of newly diagnosed GBMs. In the trial, patients with newly diagnosed GBM expressing EGFRviii will undergo resection and standard concurrent chemo-radiotherapy with TMZ. Patients will then be vaccinated with purified synthetic EGFRviii-KLH along with the adjuvant GM-CSF starting two weeks after completing radiotherapy, and then every two weeks for four cycles. Patients will then receive standard maintenance TMZ therapy along with additional vaccination on day 21 of each 28-day cycle of TMZ until intolerance or disease progression.

This protocol proved effective in preclinical studies as well as in a multi-institutional phase II study. In the phase II trial, which involved 23 patients, the median time to progression of patients receiving treatment increased by 70% compared to historical controls (12.1 months vs. 7.1 months; $P < 0.006$), and median survival was more than 19 months. Toxicity was limited to local inflammation at the injection site, and 62% had evidence of an immune response to the vaccine.

The second trial, DC-Vax, is a customized vaccine made by expanding dendritic cells from the patient's own blood and loading them with tumor lysate made from the patient's own tumor. The vaccine is also administered subcutaneously. Patients with newly diagnosed GBM are eligible regardless of the degree of EGFRviii expression in their tumor. As in CDX-110 vaccine, patients will undergo resection followed by concurrent TMZ and radiotherapy as per the standard of care. They will then receive three vaccinations of autologous DC-Vax prior to beginning TMZ maintenance therapy. Thereafter, each patient will receive additional vaccines on week three of every four-week TMZ maintenance therapy cycle. A phase II study in 12 patients with newly diagnosed GBM demonstrated median time to progression of 18.1 months with median survival of 33.8 months, and six patients have demonstrated no evidence of disease progression with followup between eight and 27.5 months. Toxicity was minimal, and no evidence of autoimmune response was noted, while four of six patients demonstrated evidence of an antitumor immune response.

Additional NIH-funded studies on brain tumor vaccines are ongoing at UH's Neurological Institute and Ireland Cancer Center, which have developed an expertise in this area.

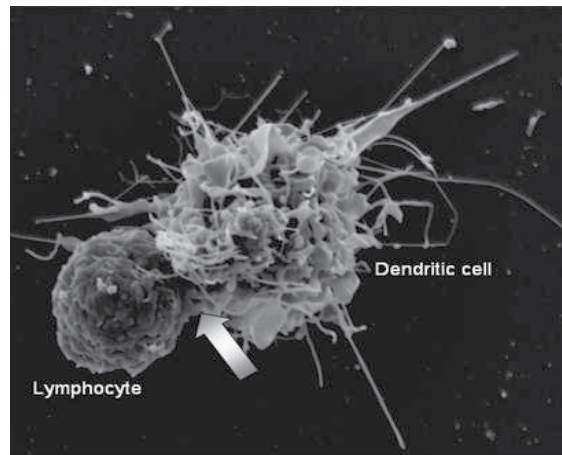


Figure 3 – Dendritic cells (DCs) are monocytes specialized for antigen presentation. DCs have multiple spindle-like arms (dendrites) rich in immunological co-stimulatory molecules which increase their surface area and their avidity for lymphocytes. This increases interaction between the two cell types and induces activation of the T-lymphocyte.

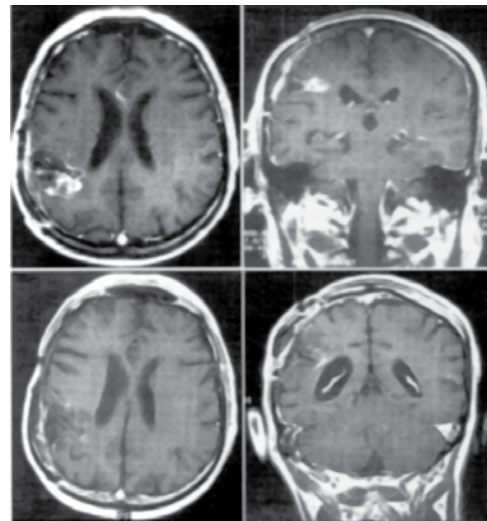


Figure 4 – Tumor vaccines have been demonstrated to induce tumor regression. The patient illustrated in this photograph had recurrent GBM (top row) which responded to immunotherapy (bottom row).

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Dr. Sloan reports no financial interest relevant to this article.

Trigeminal Neuralgia: Innovative Treatment Options Abound

By Robert J. Maciunas, M.D., MPH, FACS

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 including 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.⁴ Atypical face pain (AFP) is predominantly constant, and may not be confined to the trigeminal sensory distribution. Denervation 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.⁵

Many patients with typical idiopathic trigeminal neuralgia demonstrate compression 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.^{6,7,8} This is most commonly caused by adjacent vessels, especially the superior cerebellar or anterior inferior cerebellar arteries, or less often, nearby veins. Injury to the trigeminal nerve results in ephaptic transmission of pain.⁹ Trigeminal neuralgia symptoms may also be associated with intracranial tumors affecting the trigeminal nerve or multiple sclerosis.^{6,10}

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.¹² Over 10 years of followup, however, only 56% of patients maintain satisfactory pain relief with

Dr. Maciunas and radiation oncologist, Douglas Einstein, M.D., Ph.D., position a patient with refractory trigeminal neuralgia for treatment with Gamma Knife radiosurgery.



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(Trigeminal Neuralgia continued)

medical therapy.¹³ 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 Horsely in 1891.¹⁴ 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. Stookey 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 29%, with severe paresthesias in 10%.^{15, 16}

In 1925, Walter Dandy described a posterior fossa approach for sectioning of the posterior sensory roots of the trigeminal nerve at the pons.¹⁷ This partial section of half of the sensory root sought to avoid loss of corneal sensation and resultant keratitis. The anterosuperior motor nerve was left intact. Interestingly, Dandy noted a frequent association of an ecstatic vascular loop compressing and distorting the trigeminal nerve adjacent to the pons.¹⁸ In his series of 500 patients, Dandy reported that only six experienced recurrences.¹⁹ 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% and good results in 8%, often at the price of more sensory loss and dysesthetic sequelae.²⁰

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 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 90 to 95%, and the incidence of delayed recurrence is about 22%.²¹ 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.²² 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.²³

Barker et al reported on the experience of Peter Jannetta at the University of Pittsburgh in performance of 1204 MVD surgeries.²⁴ 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%.²⁵

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.^{21,26,27}

Gamma Knife Radiosurgery

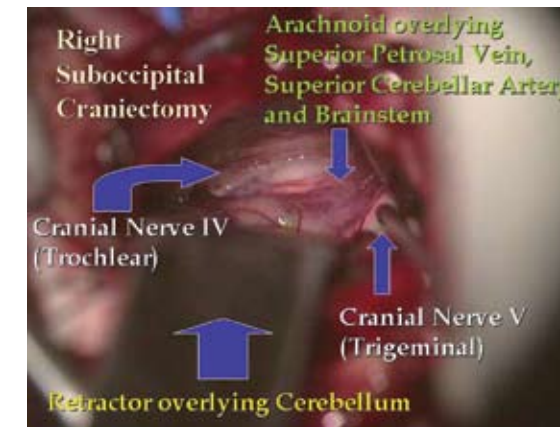
Leksell first targeted the Gasserian ganglion with radiosurgery for trigeminal neuralgia in 1951.²⁸ Inconsistent results led Lindquist and Rand to conclude that the ganglion was not an optimal target.^{29,30} With the targeting of the trigeminal nerve adjacent to the pons, superior results have been 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.³¹⁻³³ 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 perhaps 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 anesthesia dolorosa, and no reported mortality.^{32,34}

In 1996, a multicenter study evaluated Gamma Knife radiosurgery targeting the proximal trigeminal nerve near the pons.³¹ 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.³⁵ 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.³⁶

Massager et al retrospectively compared three treatment groups: Gamma Knife surgery to the retrogasserian trigeminal nerve root with less than 90 Gy, with 90 Gy, or 90 Gy plus selective beam channel blocking.³⁷ The portion of the trigeminal nerve targeted was anterior to the Obersteiner-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



Microsurgical anatomy of the approach to the right ventrolateral brainstem and cranial nerves.



Compression of the trigeminal nerve root entry zone by an ecstatic arterial loop.

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 an increased incidence of mild dysesthesias from 15% to 21% to 49%, and that of bothersome dysesthesias 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 sclerosis have demonstrated lower success rates and more frequent recurrences 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.^{32,34,38}

GKS provides a means for a good likelihood of therapeutic benefit and an extremely low risk of complications in patients unwilling or unable to undergo other surgical procedures for TN.³⁹ Investigators using linear accelerator (LINAC) stereotactic radiosurgery systems have reported comparable results for treating TN, although with slightly lower success rates and slightly higher complication rates than GKS.^{15,36}

Percutaneous Radiofrequency Rhizotomy

Kirschner performed electrocoagulation of the Gasserian ganglion in 1932.⁴⁰ Complications due to uncontrolled heat spread limited acceptance of this procedure. White and Sweet refined this technique to include short-acting anesthetics that allowed patient awakening during surgery for sensory testing, electric stimulation for more precise localization in the ganglion, radiofrequency current for lesion production, and temperature monitoring for lesion control.⁴¹⁻⁴³ Additional refinements by Tew and Taha and Nugent included the use of a curved radiofrequency needle to access individual nerve distributions.⁴⁴⁻⁴⁷ Letcher and Goldring demonstrated that the A-delta 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.⁴⁸

Radiofrequency rhizotomy (RFR) is a widely used technique that carries low risk to the patient, and can be repeated if necessary.²⁶ In this surgical procedure, a curved radiofrequency thermocoagulation 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 pupil, and the site of needle insertion 2.5 centimeters lateral to the oral commissure.⁴⁹ A 100 millimeter 20 gauge stylet with cannula is inserted toward the first two landmarks. On submental vertex fluoroscopy, the needle is directed to the medial foramen ovale. On lateral fluoroscopy, the needle is aimed toward the angle of the clivus and the petrous bone shadows, 5 to 10 millimeters below the sella floor along the clivus, about 6 to 8 centimeters deep to the point of insertion. Short-acting intravenous methohexital anesthesia is used during needle insertion into Meckel's cave, which is greeted by a wince and contraction of the masseter muscle. Cerebrospinal fluid may be noted to flow from the needle, although patients with previous percutaneous procedures may not demonstrate this.

The curved needle is situated 5 millimeters proximal to the clivus and directed caudally and laterally for V3 pain; at the clivus for V2 pain; and 5 millimeters distal to clivus and directed cephalad and medially for V1 pain. The carotid artery is at risk of penetration by the needle, which would result in termination of the procedure. A reference electrode is placed in the scalp at the hairline. Initial testing with the patient awake allows selective positioning of the needle tip in the affected

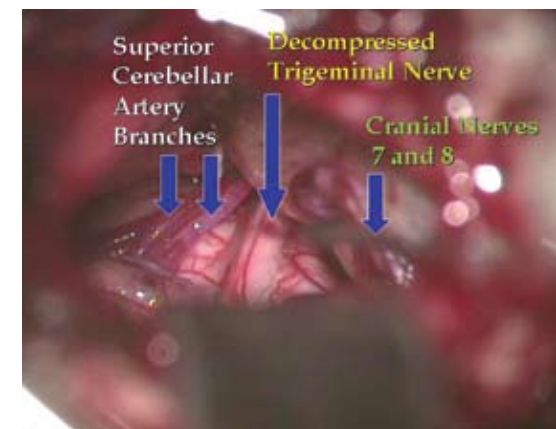


Microvascular decompression of the trigeminal nerve.

root. Mild heating (less than 40°C) or square wave current of 0.2 to 0.3 volts at 50 Hz and 0.1 msec duration produces paresthesias in the distribution of the targeted nerve. Additional short-acting anesthetic then allows for the thermocoagulation to be accomplished. A preliminary lesion is produced at 70°C for 70 seconds (for V1, 60°C for 60 seconds). A facial flush is seen, due to antidromic release of vasodilatory peptides (substance P and calcitonin gene-related peptide).⁵⁰ Repeat lesions are created, increasing the temperature by 5-10°C and the duration by 5-10 seconds, until the desired effect is achieved.

Dense hypalgesia without analgesia in the primarily affected nerve divisions, and inability to reproduce trigeminal pain by touching the known trigger points, is the endpoint. Decreasing the degree of sensory loss will result in a lower incidence of dysesthesias. However, the long-term success rate is directly related to the degree of numbness produced by the procedure. Dense hypalgesia may be undesirable in patients with V1 trigeminal neuralgia, or in the occasional patient with pain affecting all three divisions of the nerve, leading to acceptance of earlier recurrence of pain or selection of another therapeutic procedure.

The initial success rate for pain relief after radiofrequency rhizotomy is 90% or better. The delayed recurrence rate is approximately 15-30% over 10 to 15 years, if dense hypalgesia has been achieved at surgery. The mortality rate for this procedure is less than 0.1%. The close association of the internal carotid artery must be kept in mind when initially positioning the needle. Morbidity includes dysesthesia (6-22%), anesthesia dolorosa (0.2-12%), corneal anesthesia and keratitis (3-7%), diplopia (1%), transient trigeminal motor impairment (18-43%), and meningitis (0.3%).⁵¹⁻⁵³



Decompressed trigeminal nerve root entry zone.

Radiofrequency rhizotomy is effective for facial pain related to intracranial tumors and for patients with multiple sclerosis. It has been reported to benefit patients with cluster headaches, although the resulting decrease in corneal sensation requires ongoing eye care.

Percutaneous Glycerol Rhizotomy

Therapeutic injections into the trigeminal cistern have been reported since 1910; Harris achieved pain relief with alcohol at the cost of anesthesia and the risk of multiple cranial neuropathies. In 1981, Hakanson discovered that injection of glycerol into the trigeminal cistern alone was sufficient to produce relief of neuralgia. The glycerol had been employed to carry tantalum in order to target the Gasserian ganglion with Gamma Knife radiosurgery.⁵⁴

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.⁵⁵ 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.⁵⁶

Persistent 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%.^{57,58}

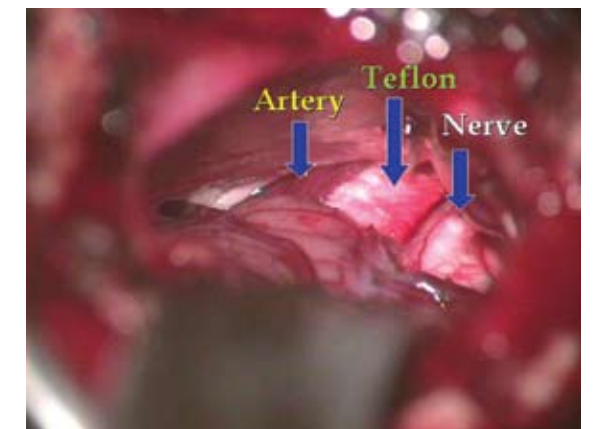
The technique of needle placement follows that of Hartel and of Hakanson.^{54,49} A 20 gauge spinal needle is placed into the trigeminal cistern through the foramen ovale. CSF flow from the needle in this position is highly desirable but not required. Some surgeons perform cisternography to assess the volume of Meckel's cave, while others presume a volume of less than or equal to 0.25 milliliters. After injection, the needle is removed and the patient is maintained for two hours in a semi-sitting position to prevent escape of glycerol into the posterior fossa.⁵⁹

Percutaneous retrogasserian glycerol rhizotomy has a high initial success rate, although it shows a higher recurrence rate than does radiofrequency rhizotomy. The degree of pain relief with PRGR is not directly related to the degree of hypesthesia, and the incidence of severe sensory loss and anesthesia dolorosa is lower than that for radiofrequency rhizotomy. Because PRGR is easily repeated, some practitioners prefer this technique because of its lessened risk of sensory deafferentation.

Percutaneous Balloon Compression

In 1983, Mullan and Lichtor described a treatment for trigeminal neuralgia that employed compression of the trigeminal nerve by a percutaneously placed balloon catheter.⁶⁰ Under general endotracheal anesthesia, a blunt cannula is inserted up to the foramen ovale. A guiding stylet is advanced through the cannula to the target and then removed. A balloon catheter with an inner wire stylet is inserted under fluoroscopic guidance. The balloon is inflated to a pressure of 1100 mmHg or 1.3-1.5 atmospheres, using approximately 1 milliliter of contrast dye, for one minute. The balloon is then deflated and removed along with the sheath.

An external cardiac pacemaker is typically necessary to rapidly prevent the intraoperative bradycardia and arrhythmias seen in two-thirds of patients during balloon compression. Ninety-three percent of patients obtain initial relief of their face pain. Recurrence of pain over 4½ years was seen in 25%. Repeat percutaneous balloon compression was associated with a 68% success rate. A lessened incidence of corneal anesthesia in patients with V1 distribution trigeminal neuralgia has been advocated as an advantage to this procedure. In a series of 236 percutaneous balloon compression surgeries with 37% involving V1 division pain, numbness was seen in 61%: mild in 80%, moderate in 14%, and severe in 6%. Corneal anesthesia and anesthesia dolorosa occurred in less than 1% of patients. Motor trigeminal nerve function is interfered within 19%, with jaw muscle weakness persisting as long as a year.⁶¹⁻⁶³



Teflon pledget maintains microvascular decompression.

Trigeminal Neurectomy

Peripheral destructive procedures for trigeminal neuralgia were described by Schlichting in 1748, and Marechal and Andre in 1732.³ Supraorbital, infraorbital, and inferior alveolar neurectomy have proven beneficial in patients who have failed other surgeries or who are elderly or medically unable to undergo another procedure.

Supraorbital and infraorbital neurectomy typically are employed to avoid the risk of keratitis otherwise associated with V1 with or without V2 numbness. Neurectomy is relatively easy to perform and is associated with a low incidence of mortality or morbidity. Pain relief in the distribution of the profound anesthesia is typical, with an average duration of two to three years.⁶⁴⁻⁶⁷

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

Stereotactically directed lesioning procedures treating refractory facial pain have targeted the trigeminal nucleus caudalis, the trigeminal tract, the anterior limb of the internal capsule, and the cingulate gyrus.⁶⁸⁻⁷⁰ Deep brain stimulation of the periaqueductal gray and periventricular regions has been advocated for chronic pain syndromes.^{39,71}

In 1967, Shelden et al first attempted selective Gasserian ganglion electric stimulation for trigeminal neuralgia by the subtemporal implantation of a plate electrode in Meckel's cave that was connected to a subcutaneous pulse generator.⁷² Subsequently, electrodes became available for percutaneous insertion into Meckel's cistern. Broggi reported on 21 patients with chronic hemifacial pain undergoing this procedure. Seven patients had postherpetic neuralgia, five patients had anesthesia dolorosa, and two had post-traumatic peripheral nerve injury. An initial test electrode was implanted and treatment results assessed before permanent system implantation in 14 patients. After two years, only one patient continued to derive benefit from stimulation.⁷³ On the other hand, Steude reported successful results in patients permanently implanted after positive test stimulation for neuropathic facial pain (approximately one out of two cases): 40/47 patients (86%) with post-dental surgery chronic pain, 11/12 patients (92%) with chronic posttraumatic facial pain, and 13/13 patients (100%) with anesthesia dolorosa after surgery for trigeminal neuralgia. Postherpetic neuralgia never benefited from electrical stimulation. Trigeminal neuralgia proved an inappropriate indication for this procedure, because electrical stimulation itself would provoke pain attacks.⁷⁴⁻⁷⁶

Transdural stimulation of the precentral gyrus motor cortex has been advocated for anesthesia dolorosa, post-traumatic neuropathy and postherpetic neuralgia. Central pain after cerebrovascular accidents has been less responsive to this treatment. Intraoperative stimulation in an awake patient is required to position the epidural quadripolar electrode through a burr hole craniotomy.⁷⁷⁻⁷⁹

Toward a Treatment Paradigm for Trigeminal Neuralgia

First and foremost, the diagnosis of TN must be carefully and definitively established. The initial treatment of TN remains the prescription of an appropriate sequence of medications to either achieve relief, or to establish therapeutic failure or intolerance. Medically refractory TN should be treated with a neurosurgical procedure. Patients should be thoroughly and honestly informed of all potential surgical options, the attendant risks, and expected outcomes. The neurosurgeon and patient together must form a therapeutic alliance to successfully arrive at the optimal surgical approach to medically refractory trigeminal neuralgia.

In this context, it is often considered appropriate to offer MVD as an option to all healthy patients less than 70 years of age, because of its high success rate and nondestructive nature. Some patients who fail to manifest vascular compression at surgery might be considered candidates for selective trigeminal sectioning. In patients who are unwilling to under go MVD, who are older than 70 years

of age or who have significant medical conditions that increase their surgical risk, an alternative recommendation may be GKS. This 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 wish 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 section or peripheral neurectomies.
- Patients whose pain recurs after a second GKS, or those who failed to secure initial benefit after a GKS, may be offered RFR, PRGR, PBC, selective trigeminal section or peripheral neurectomies.

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, there is no entirely satisfactory therapy for this denervation dysesthesia with its attendant suffering. This must be borne in mind by the surgeon whenever approaching treatment of a patient suffering from the benign although intolerable disease of medically intractable trigeminal neuralgia.



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Evaluation of Memory Dysfunction

By Alan J. Lerner, M.D.



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 amnesic 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 inability to incorporate new information. Many other structures are now known to be involved in memory formation, including components of the motor system, limbic structures, frontal and prefrontal cortices and frontal-subcortical pathways. Therefore, memory dysfunction is not a good localizing finding but is of prime functional importance in assessing neurological abilities and disabilities.

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 anomia 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,³ 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.^{1,2,4} 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.

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 foggy 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.

MEMORY AND COGNITION CENTER

Alan J. Lerner, M.D., Director

The Memory and Cognition Center has a 20-year track record of providing exemplary care for those affected with disorders of memory and cognition (mental processes). The internationally known specialists here manage both the medical aspects of memory and cognitive disorders, and the emotional and family issues often a part of these diseases.

Our staff works closely with the Neurology Department at Case Western Reserve University School of Medicine and has access to research sponsored by the National Institutes of Health as well as the pharmaceutical industry.

Conditions we treat include Alzheimer's disease, vascular dementia, frontotemporal dementia, dementia with Lewy bodies, mild cognitive impairment, Parkinson's disease, dementia, Huntington's disease, adult autism, adult ADHD, and trisomy 21 (Down syndrome).



An individual being tested for memory loss using a word-list learning task in a clinical research study at the Memory and Cognition Center.

Standardized mental status tests, such as the Mini-Mental State Examination (MMSE), are commonly used as part of cognitive testing. The memory portion of the MMSE focuses on orientation and the registration (working memory aspect) and recall of three words (early long-term memory). Particularly early in the course of many illnesses, this may be insensitive and a recent study found that almost 50% of people forgot at least one of the three words.

A number of simple tests can supplement the MMSE and have been shown to correlate well with it. The patient is asked to register a five-item memory phrase ("John Brown, 42 Market Street, Chicago"), and is given three chances for registration. The clinician then allows for a period of distraction, for instance, while obtaining additional history or performing some aspect of the neurological examination. The patient is then asked without specific cuing to recall the name and address mentioned.

Implicit and semantic memory can be examined by discussion of current news and events. It may be necessary to provide cuing, such as asking about the location of a natural disaster or war, but the information gained makes this a worthwhile procedure. Semantic memory is also assessed by testing lexical or category fluency, for instance giving the patient 60 seconds to name items in a category, such as animals or words that begin with the letter "F".

Office procedures are intended as screening, and particularly when supplemented with more sophisticated neuropsychological evaluation, help point to cognitive domains and anatomical areas suspected to be dysfunctional. If there is doubt about either the presence of a memory disorder or

its significance, or its relationship to other cognitive deficits, neuropsychological evaluation is recommended. Neuropsychological expertise can help determine if test anxiety or other psychological factors such as depression play a role in test performance. This type of testing also can ferret out whether other domains, such as attentional or executive functions, are also impaired.

When the test results are integrated with neuroimaging and other clinical and laboratory data, a more specific or localized diagnosis may be possible. Lack of an obvious lesion or other predisposing cause by history, physical or laboratory testing in an individual with clinically significant memory disorder should suggest the possibility of a primary degenerative dementia.

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 wide 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.⁵ This may occur in an isolated amnesic form, but multidomain and nonamnesic 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 deterministic genes 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) e4 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

Early in the course of AD, several salient features may be present. Contrary to popular opinion, awareness of the disorder is common, but it is not a diagnostic criterion. There is also relative preservation of the "social self." Because the patient may seem oriented and interacts normally in a social situation or physician encounter, casual observation may not detect memory difficulties beyond "what is normal for my age." Studies have shown that family members are extraordinarily good at detecting cognitive changes. On average, there is a 90% sensitivity for detection of cognitive impairment, such that it behooves a physician to take these complaints seriously when advanced by a spouse or child or other close relative. Conversely, family members are somewhat less reliable when they report that a relative is cognitively "normal."

While memory deficits are the sine qua non of Alzheimer's disease, memory impairment is not sufficient to make the diagnosis as discussed above. Impairments in executive functioning, language, praxis or agnosia are required for the diagnosis by DSM-IV criteria. In the absence of defined biomarkers with

increased specificity and sensitivity over clinical assessment, the traditional method of patient evaluation remains central to the process of diagnosis. Current research initiatives such as the National Institutes of Health-supported Alzheimer's Disease Neuroimaging Initiative promise to provide longitudinal data on the stability and usefulness of biological markers, including cerebrospinal fluid indices of total tau protein, amyloid beta 40 and 42 levels, and magnetic resonance and positron emission tomographic imaging indices of brain structure and function.

Treatment of Memory Disorders

A detailed review of treatment for memory disorders is beyond the scope of this review. Cholinesterase inhibitors and N-methyl-D-aspartate (NMDA) receptor antagonists have been approved by the Food and Drug Administration for use in AD. Research into usage in other conditions is incomplete but shows some promise in areas such as traumatic brain injury, vascular dementia and Parkinson's disease dementia. The primary role of behavioral manipulations, repetition of messages and implicit understanding by an empathic physician or family member cannot be overstated.



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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.

Above: Intraoperative electrocorticography is used to refine definition of epileptogenic zone surrounding temporal lobe pilocytic astrocytoma.



Adult Epilepsy Mostly Idiopathic

The primary generalized epilepsies presenting to adult neurologists are often idiopathic with normal neuroimaging. These are predominantly genetic with the underlying pathophysiology involving mutations of neurotransmitter or voltage-gated ion channels (such as voltage-dependent sodium or potassium channels, and GABA-A or acetylcholine receptor channels). Seizure semiology, the behavioral manifestations of seizures, may include absence, myoclonic, tonic and atonic seizures. About 20% of adult epilepsies are primary generalized, and these often carry an excellent prognosis, but require specific antiepileptic drug (AED) selection. Symptomatic generalized epilepsies do exist but are usually associated with severe brain dysfunction, such as West syndrome or Lennox-Gastaut syndrome, or with injury early in life.

In contrast, partial epilepsies are characterized by focal onset seizures. On magnetic resonance imaging, the area of seizure onset may be associated with gross structural abnormalities on MRI such as a stroke, tumor, vascular malformation or encephalomalacia and gliosis secondary to trauma. However, though seizure semiology and EEG may indicate a partial epilepsy, until recently magnetic resonance imaging has only shown a corresponding lesion in a little over half of cases.

The majority of adult focal epilepsies, about 60%, arise from the temporal lobe. Another 20% arise from the frontal lobes, with the remaining 20% split between parietal and occipital lobes. Most focal epilepsies can be controlled with antiepileptic drugs. However, once a patient fails two antiepileptic medications, the likelihood of success with another AED is only about 5%,¹ making these patients pharmacoresistant or medically intractable. A recent study by Wiebe showed the superiority of epilepsy surgery compared to additional AED trials for medically intractable temporal lobe epilepsy. Standard en bloc temporal lobectomy resulted in about 60% of study subjects becoming seizure free.² The only death in this study occurred in the medically managed group secondary to a seizure. Sudden unexpected death in epilepsy (SUDEP) would be expected to occur at a rate of about one in 300 medically intractable patients per year.³

Mesial Temporal Sclerosis Common

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.⁶ 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.⁴ MTS may also develop in adults after trauma or status epilepticus.⁵ 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 2004⁷ 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: dysembryoplastic neuroepithelial tumors (DNTs) 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.

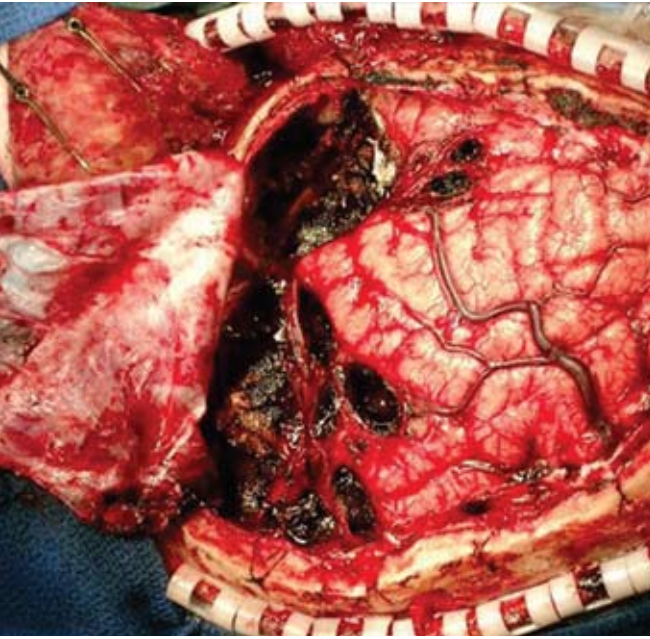
Results of extraoperative electrocorticography with subdural grids, defining epileptogenic zone and functionally eloquent cortex in a case of frontotemporal cortical dysplasia.



EPILEPSY CENTER

Hans O. Lüders, M.D., Director

At the Epilepsy Center, our epileptologists and other professionals have the experience, skill and knowledge to help adults and children (in partnership with Rainbow Babies & Children’s Hospital) with epilepsy lead more comfortable, fulfilling lives. Our center is ranked Level IV, the highest designation recognized by the National Association of Epilepsy Centers. We offer state-of-the-art medical and surgical treatments, and vagus nerve stimulation. Our researchers have contributed to the discovery and development of numerous effective therapies for epilepsy, including medications and surgical techniques.



Intraoperative photograph after resection of epileptogenic frontotemporal cortical dysplasia.

Microdysgenesis in the temporal lobe is typically only of Type 1A (52/56 cases reported by Widdess-Walsh et al).⁸ The 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%.⁹

Cortical Dysplasia in Epilepsy

The incidence of cortical dysplasia in epilepsy surgical series has ranged from 12-40%.¹⁰ 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 3.¹¹

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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Recurrent Lumbar Disc Herniation: Assessment of Management Choices

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 laminectomy 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 40% 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. Cauchoix et al reported that in 520 patients treated with discectomy, only nine (1.7%) required fusion one to 20 years after initial discectomy. Thirty-one (6%) patients in this series were treated for recurrent disc herniation. Gill and Frymoyer 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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Deep Brain Stimulation for Tourette Syndrome

By:

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Mike R. Schoenberg, Ph.D., ABPP-CN

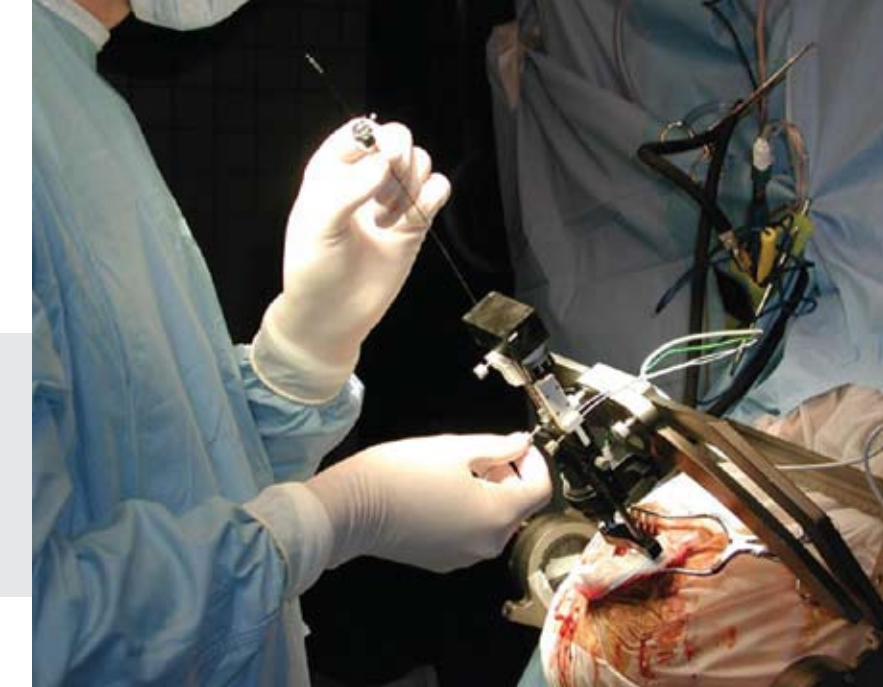
Christina Whitney, RNCS, DNSc

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Tourette Syndrome, the Clinical Entity

Tourette syndrome (TS) is a disorder in which individuals randomly but repeatedly produce stereotyped behaviors (tics) of any part of the body, including sound production. Affected individuals commonly describe an irresistible "urge" which is relieved upon performance of the tic (suppression may be transiently successful). An association with comorbid psychiatric disorders in pediatric patients is well described. These include attention deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), depression, and anxiety.¹



Insertion of microelectrode for intraoperative mapping of basal ganglia.

The mean onset of symptoms is about 5 years of age, and greatest tic severity occurs around 10 years.² 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.¹ 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.³

Anatomic, Physiologic and Pharmacologic Substrate of TS

The etiopathology of TS is not yet clear. Genetic transmission is well documented.^{1,4} 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),⁵ 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 antidopaminergic agents could suppress tics.⁶ 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.⁷⁻⁹

Models of basal ganglia interconnections and function have been evolving¹⁰⁻¹³ 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

(DBS for Tourette Syndrome continued)

parallel pathways arriving 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.^{10,12} 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 behaviors^{12,13} and may explain the high incidence of obsessive-compulsive symptoms (OCS) and behaviors (OCB). Certain aspects of OCS/OCB in TS are sufficiently distinct from those of OCD¹ to suggest separate pathophysiologic origins.



Intraoperative neurologic examination during microstimulation of the thalamus.

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 catecholamine depletors (reserpine, tetrabenazine), or central alpha-2 adrenergic receptor blockade (clonidine).¹³ 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.³ 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.¹³ 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 incerta.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 sonic 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)¹⁵ reported on six patients with severe motor tics who received significant benefit from staged bilateral ventrolateral (VL) thalamotomies. Hassler and Dieckmann (1982)¹⁶ reported on 15 patients with excellent, durable clinical results after undergoing bilateral thermocoagulation of the rostral intralaminar nuclei and medial thalamic nuclei. de Divitiis et al (1977)¹⁷ 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)¹⁸ 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,¹⁹ targeting the ventral thalamus bilaterally. The first of these cases had been reported by Vandewalle et al (1999).²⁰ These authors carefully considered the existing lesion-based reports and determined that the targets of Hassler and Dieckman 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.¹⁴ 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)¹⁶ and Visser-Vandewalle et al (2003)¹⁹ 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 procedure.²¹ That 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

MOVEMENT DISORDERS CENTER

David E. Riley, M.D., Director

The Movement Disorders Center provides a full range of diagnostic and therapeutic capabilities for neurological movement disorders. We have the longest-running active practice devoted solely to movement disorders in the state of Ohio. We care for patients with any kind of disorder that causes involuntary movements, including Parkinson's disease, essential tremor, Huntington's disease, Tourette syndrome, dystonia (generalized or focal, including torticollis, blepharospasm, writer's cramp, oromandibular dystonia, spasmodic dystonia), and hemifacial spasm.

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),¹⁹ one by van der Linden et al (2002),²⁴ one by Houeto et al (2005),²⁵ one by Ackermans et al (2006),²⁶ six by our group^{21,22} and eighteen by Porta et al (2006).²⁷ 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 (YGTSS).²⁸ 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-Pf) nuclear complex.¹⁴ This is given with respect to the midcommissural point as 5mm lateral, 4mm posterior, and 0mm inferior.¹⁹ However, the active target in DBS is not necessarily the tip contact of the electrode, as there are four electrodes to choose from over a span of 10.5mm along the trajectory (labeled from tip to more proximal contacts as 0, 1, 2 and 3). One may be able to identify the thalamic regions through which the electrode must pass (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.^{25,26,29,30} As with thalamic stimulation, outcome measures have included tic frequencies, YGTSS 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)²⁵ explicitly targeted "limbic pallidum." This approach and target are sufficiently distinct that one GPi territory is not covered by the other. The number and positions of the active electrodes varies, and it is not yet clear which pallidal target is most efficacious. It should be pointed out that for dystonic disorders treated by DBS (GPi target), the nuclear territory is relatively large, the amount of energy required to control symptoms is also large, and the stimulator battery life is correspondingly shorter. This may be a disadvantage if patients require more frequent surgical replacement of the neurostimulators. Whether this situation applies to TS is not yet known.

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. Less success was apparent in a single case report of implantation of bilateral DBS electrode tips in the nucleus accumbens and contacts along the anterior limb 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,³¹ 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 limb of internal capsule have been proposed as targets for treatment of OCD.³² 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 en passage, is plausible.

Prospective Surgical Trial

Sufficient data exist to suggest that DBS is worth exploring as a possibly efficacious treatment for medically refractory TS. However, most data are derived from case reports, case series, open label trials, "n of 1" studies and our own pilot double-blind randomized controlled trial of five subjects.²² As can be appreciated from the foregoing discussion, many questions remain unanswered.

Preliminary analysis of our pilot study data suggests a significant benefit from 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 compatible with recently published standards for design and conduct of a trial of DBS.

Intraoperative microelectrode recording from basal ganglia.



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- 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.
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