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Outcome Predictors of Pallidal Deep Brain Stimulation for Dystonia

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More than a decade of clinical research has established that deep brain stimulation (DBS) of the globus pallidus internus (GPi) is a safe and effective treatment for advanced, disabling dystonia.^{1,2} Dystonia is a movement disorder characterized by patterned, directional and often sustained muscle contractions producing abnormal postures or repetitive movements that are often disabling.³ Despite the recognized and at times “miraculous” role of DBS in the treatment of advanced dystonia, the indications for pallidal stimulation remain highly empirical. Current experience suggests that primary dystonia responds better than most secondary dystonias, and patients carrying the DYT1 genetic mutation appear to be particularly good candidates.⁴ However, with the exception of DYT1 carriers, it has been typically difficult to identify those patients with dystonia who will respond best to DBS because of poorly defined predictors of outcome.

In order to define demographic and clinical outcome predictors of pallidal stimulation for primary dystonia, large and homogeneous study populations are needed. To this purpose, we reviewed DBS results obtained in our large cohort of primary dystonia patients.* In a first study, we found that younger age at surgery is associated with better outcomes one year after the implant of DBS electrodes.⁵ In a second paper, reviewing the clinical records of 39 consecutive patients with medically refractory primary dystonia who underwent pallidal DBS, we came to slightly different conclusions. In this population, the only clinical feature predicting DBS outcome one year after surgery was the duration of dystonia. Patients with shorter duration of disease had a better general outcome, independent of their age.⁶

We know that improvement of dystonic symptoms after pallidal DBS is characteristically delayed, progressing over several months and more than one year in some patients. Therefore, we further investigated the magnitude of improvement beyond the first year of therapy and tested whether clinical

features that are predictive of outcome at one year remain so in the longer term. In order to determine if these factors are significant in a wider clinical experience, we collected data from five established DBS centers in Europe and the United States. All 44 subjects included in the study showed a distinct improvement after DBS implants (74.9% at one year and 82.6% at three years), which correlated both with disease duration (DD) and age at surgery in an unexpected fashion. We clustered our population into three groups:

1. Younger subjects (<27 years) with shorter DD (≤ 17 years)
2. Older subjects (>27 years) with shorter DD (≤ 17 years)

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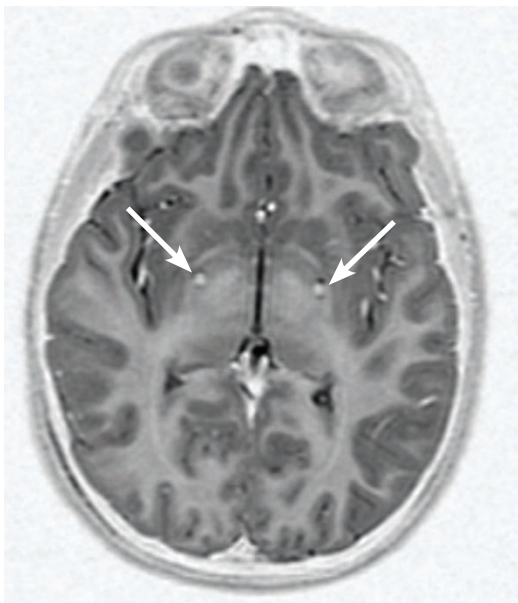


Figure 1: Postoperative axial brain MRI showing bilateral DBS electrode placement (arrows) in the globus pallidus internus of a patient with intractable generalized dystonia.

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Improving Brain Metastases Outcomes

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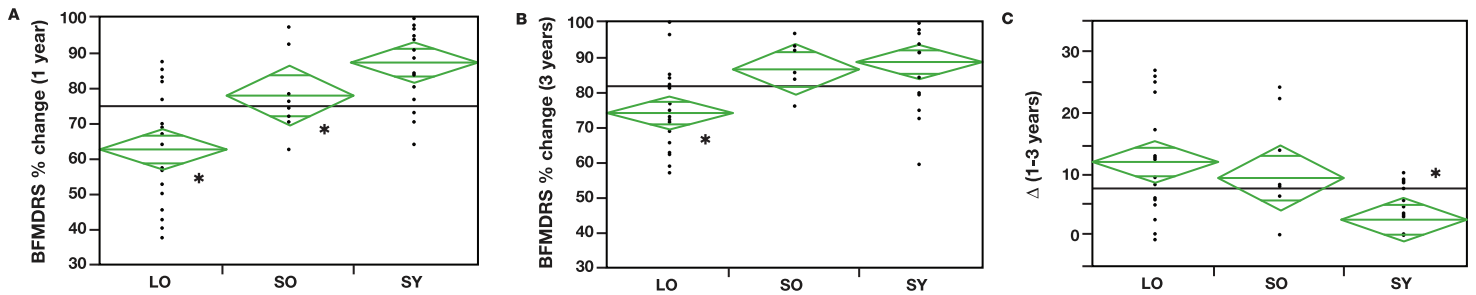


Figure 2: Differential outcomes in age and disease duration clusters as measured by percentage change in the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS). Younger patients with short disease duration (SY) showed better outcome both one (A) and three years after surgery (B), without a significant change between the two observations. Subjects with older age at surgery showed a significant additional outcome improvement between year one and three follow-up (C). Originally published in *Journal of Neurology*.⁷

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3. Older subjects (>27 years) with longer DD (≥17 years).

As predicted by previous studies, the first group showed best results. However, older patients surprisingly gained further benefit from DBS from 1- to 3-year follow-up (Fig. 2). We concluded that subjects with short disease duration may expect to achieve a better general outcome and that age at surgery may influence the time necessary to achieve maximal clinical response.⁷

Where to go next? Examining the roles of disease duration and age as outcome predictors is informative, but it is still an indirect approach to the main limitation of DBS. DBS mechanisms of action remain virtually unknown, making it difficult to optimize benefits and troubleshoot failures. In particular, it is unclear whether the long delay between stimulation onset and clinical improvement is due to the physiological time needed for the brain to respond to DBS, or to the empirical,

time-consuming “trial-and-error” system currently used to find optimal stimulation settings.

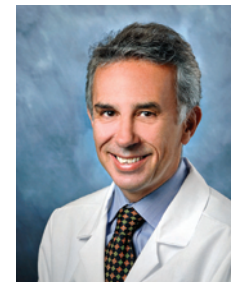
In new research that we hope to conduct at Cedars-Sinai, we intend to look for anatomical regions that may be significantly correlated with clinical improvement during DBS using a computational model to calculate volumes of neuronal tissue activated in the GPI of patients already receiving optimal stimulation. We then plan to test this data prospectively in patients undergoing implantation and observe whether a rational, scientific approach to stimulation, derived from successful outcomes, will optimize results and shorten their latency.

**Some of the human research activities described in this article were initiated at a non-Cedars-Sinai institution prior to the investigator’s arrival at Cedars-Sinai.*

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Gamma Knife: Relief for Trigeminal Neuralgia

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Trigeminal neuralgia (TN) is one of the most common and debilitating causes of facial pain. Clinically, it usually manifests as a stabbing/shooting pain originating on one side of the face and typically worsens with factors such as brushing teeth or cold weather.

The trigeminal nerve provides the sensory supply to the face and the sensory and motor supply to the muscles of mastication. It has three major divisions: ophthalmic (V1), maxillary (V2) and mandibular (V3). TN can originate from any of these, but usually occurs at V2.

The annual incidence of TN is about 10 per 100,000 people. Approximately 15,000 new cases occur in the United States each year. The incidence increases gradually with age;

most idiopathic cases begin after age 50, although onset may occur in the second and third decades or, rarely, in children.

Most cases of TN are caused by compression of the trigeminal nerve root, usually within a few millimeters of entry into the pons (the root entry zone). Compression by an aberrant loop of an artery or vein is thought to account for 80 to 90 percent of cases. Idiopathic TN or TN caused by a vascular compression is considered classic TN.

Other causes of TN via nerve compression include vestibular schwannoma (acoustic neuroma), meningioma, epidermoid or other cyst, or rarely a saccular aneurysm or arteriovenous malformation. TN caused by structural lesions other than vascular compression

is classified as secondary TN.

The mechanism by which compression of the nerve leads to symptoms appears to be related to demyelination in a circumscribed area around the compression. Precisely how demyelination results in the symptoms of TN is not entirely clear. Demyelinated lesions may set up ectopic impulse generation, possibly causing ephaptic transmission. Ephaptic cross-talk between fibers mediating light touch and those involved in pain generation could account for the precipitation of painful attacks by light tactile stimulation of facial trigger zones. Furthermore, alteration of afferent input may disinhibit pain pathways in the spinal trigeminal nucleus.

Evidence for a role of central pain mecha-

nisms includes the presence of refractory periods after a triggered episode, trains of painful sensations after a single stimulus, and latency from the time of stimulation to the onset of pain. In addition, electrophysiologic evidence of central sensitization of trigeminal nociceptive processing has been observed in patients with atypical TN who have concomitant chronic facial pain. Demyelination of one or more of the trigeminal nerve nuclei may also be caused by multiple sclerosis or other structural lesions of the brainstem. In multiple sclerosis, a plaque of demyelination typically occurs in the root entry zone of the trigeminal nerve, although vascular compression also has been noted in these patients.

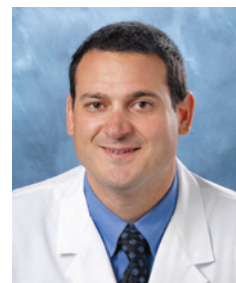
The initial management of trigeminal neuralgia is a variety of medications, including carbamazepine, lamotrigine, baclofen and others. Additional management options include rhizotomy, peripheral neurectomy and microvascular decompression. Gamma Knife® therapy produces lesions with focused

gamma radiation. The therapy is aimed at the proximal trigeminal root, since targeting the gasserian ganglion has produced poor results. The aiming of the beams is carried out with a stereotactic frame and MRI. The doses used are 70 to 90 Gy. The beams cause axonal degeneration and necrosis. Pain relief with Gamma Knife surgery occurs after a lag time of about one month.

The 2008 AAN/EFNS practice parameter identified one randomized controlled trial of Gamma Knife surgery for TN that compared two different treatment regimens and found no important differences. In addition, the AAN/EFNS identified three case series with independent outcome assessment. Complete pain relief at one year was found in up to 69 percent of patients, and at three years in 52 percent. An earlier systematic review found that approximately 75 percent of patients report complete relief within three months, but the proportion decreases to 50 percent by three years. New or worsened

facial sensory impairment occurred in 9 to 17 percent, with more bothersome sensory loss or paresthesia found in 6 to 13 percent of patients. However, anesthesia dolorosa is rarely, if ever, a complication of Gamma Knife surgery.

Overall, the results with the utilization of Gamma Knife radiosurgery as part of the management of TN has been safe and effective, and should be considered if medical therapy fails.



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Study Suggests Benefit to Screening Patients with Bicuspid Aortic Valve for Intracranial Aneurysms

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A recent case-control study lends credence to the suspicion that patients with bicuspid aortic valve (BAV) have a significantly higher than normal risk of suffering intracranial aneurysms. We found intracranial aneurysms in about 10 percent of patients who had BAV but in only 1.1 percent of a control group (*Neurology* 2010; 74:1430-33).

Bicuspid aortic valve is a common congenital heart defect, estimated to affect up to 2 percent of the population. Because it may not produce symptoms throughout most of an individual's lifetime, BAV often remains undetected until aortic valve insufficiency or stenosis appears in later years.

People with BAV are susceptible to thoracic aortic dilation, aneurysm formation and dissection—life-threatening events that often occur without warning. It was once believed that these disorders of the aorta resulted from hemodynamic changes induced by the defective valve, but we now know that the arterial structure itself is defective, making it susceptible to blood flow and pressure changes. BAV has become recognized as one of the heritable disorders of connective tissues; screening is usually suggested for first-degree relatives of those found to have the disorder.

BAV-related arteriopathy is not limited only to the aorta but also has been linked to spontaneous dissections of cervical and in-

tracranial arteries. Until now, there has been no systematic evaluation of the frequency of intracranial aneurysms among patients with BAV. Our study was designed to explore this association.

We detected six intracranial aneurysms in 61 patients (9.8%) who had been diagnosed with bicuspid aortic valve. In contrast, we found only three aneurysms in a control group of 291 consecutive patients (1.1%) undergoing magnetic resonance angiography for evaluation of unrelated disorders. In four of our six patients with BAV and intracranial aneurysms, the aneurysms measured between 2 and 4 mm in diameter. Two of the patients each had a single 6 mm aneurysm.

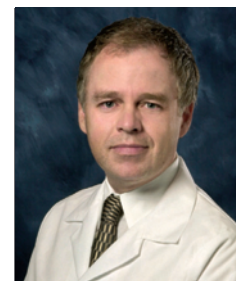
Intracranial aneurysms are slightly more common among women than men, and risk increases with age. In our study, the control population had a slightly higher prevalence of women, and average patient age was about six years greater. The fact that these risk factors were underrepresented in our BAV population supports the validity of our findings. However, dilation of the ascending aorta and root was more common among our patients with BAV than in most such series, indicating that these patients may have had more severe disease than average.

At 9.8 percent—about 10 times that of our control group and the general population—the frequency of intracranial aneurysms in

patients with BAV is similar to that found in those with two other systemic disorders: autosomal dominant polycystic kidney disease (ADPKD) and coarctation of the aorta. Five to 15 percent of patients with ADPKD have intracranial aneurysms, as do about 10 percent of patients with coarctation of the aorta.

Because of these known risks, patients diagnosed with either of these conditions are typically screened for intracranial aneurysms. ADPKD has an estimated prevalence of 1:500 to 1:1,000 in the general population, and coarctation of the aorta is estimated at 1:1,000. The prevalence of BAV is much higher, estimated at 1:50 to 1:200.

Screening BAV patients for intracranial aneurysms could potentially offer a significant diagnostic and preventive benefit, especially if additional and larger studies confirm our results.



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Improving Outcomes for Brain Metastases Patients

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Brain metastases are the most common intracranial tumors in adults. They occur in 20 to 40 percent of cancer patients, with more than 220,000 new cases diagnosed each year in the United States alone. The incidence of brain metastases is increasing due to both improved detection of small metastases by magnetic resonance imaging (MRI) and better control of extra-cerebral disease resulting from improved systemic therapy. Brain metastases occur most frequently in patients with lung cancer. Up to 25 percent of patients with lung cancer have brain metastases at diagnosis and 40 to 50 percent develop them during the course of their disease. Other cancers that commonly metastasize to the brain include breast cancer, melanoma and renal cell carcinoma.

The role of radiosurgery, WBRT

Brain metastases are managed by a combination of surgery, radiosurgery, whole brain radiation therapy (WBRT) and chemotherapy. Several recent studies and randomized control trials are redefining and clarifying the role of surgery and radiosurgery in the treatment of brain metastases.

We recently published a systematic review on the role of up-front radiosurgery in conjunction with WBRT in the treatment of patients with one to four brain metastases.¹ This meta-analysis included studies that randomized a total of 358 patients and showed that for patients with one brain metastasis, median survival was significantly longer in the radiosurgery plus WBRT group (6.5 months) compared to the WBRT-only group (4.9 months, $P = 0.04$). Additionally, patients in the radiosurgery plus WBRT group were 3.7 times less likely to have local failure compared to patients who received WBRT alone (HR = 0.27, 95% CI 0.14 to 0.52).

Furthermore, a statistically significant improvement in performance status scores and decrease in steroid use was seen in the radiosurgery plus WBRT group. For example, unchanged or improved Karnofsky performance score (KPS) at six months was seen in 43 percent of patients in the combined therapy group versus only 28 percent in WBRT group ($P = 0.03$).¹ These results highlight the role of up-front radiosurgery in the treatment of patients with a limited number of brain metastases.

Improving cognitive outcomes

As patient survival from modern systemic therapies continues to improve, we are increasingly focused on quality of life and long-term cognitive outcomes in our brain metastases patients. The focus has shifted from merely extending survival to tailoring treatment recommendations to maximize the quality of life and improve neuro-cognitive outcomes. Radiosurgery—and, in select cases, surgery—plays a key role in achieving these important goals.

We have evidence from randomized control trials that up-front stereotactic radiosurgery alone for selected patients with a limited number of brain metastases achieves excellent local tumor control while maximizing neurocognitive function. For example, Chang *et al.* randomized patients with one to three newly diagnosed brain metastases to radiosurgery plus WBRT or radiosurgery alone.² The primary endpoint was neurocognitive function. After 58 patients were recruited, the trial was stopped after researchers found a 96 percent probability that patients randomly assigned to receive radiosurgery plus WBRT were significantly more likely to show a decline in learning and memory function at four months than patients assigned to receive radiosurgery alone. Given these results, the role and timing of WBRT must be critically assessed in order to optimize neurocognitive function and quality of life. Initial treatment with a combination of radiosurgery and close clinical monitoring is recommended as the preferred treatment strategy in select patients to better preserve learning, memory and quality of life.

Crossing the blood-brain barrier

Most systemic anti-cancer treatments do not cross the blood-brain or blood-brain tumor barrier and thus have had a limited role in the treatment of brain metastasis. Efforts in our laboratories continue to identify strategies to increase the penetration of chemotherapeutic agents into metastatic brain tumors. For example, we have shown that vardenafil, a cGMP phosphodiesterase-5 (PDE-5) inhibitor, specifically opens the blood-brain tumor barrier and allows greater penetration of chemotherapeutic agents into metastatic brain tumors. After vardenafil pretreatment, this increased uptake translates into decreased tumor volume

and improved survival in animal studies.^{3,4}

Clinical trials are currently under way at Cedars-Sinai to evaluate the effects of PDE-5 inhibitors on blood-brain tumor barrier permeability as assessed by dynamic contrast enhanced magnetic resonance imaging (DCE MRI). We are recruiting patients with brain metastases and primary brain tumors. Patients are given a single dose of vardenafil and the effects of this PDE5 inhibitor on the blood-brain tumor barrier is assessed using DCE MRI. We are encouraged by preliminary results in two patients, but more data is necessary before drawing any conclusions. In addition, we have just started recruiting patients for another clinical trial that will involve administration of vardenafil plus carboplatin just prior to surgical resection of metastatic brain tumors. The goal of this study is to assess the increase in intratumoral concentration of carboplatin after administration of the PDE-5 inhibitor. We will update you on the results and progress of these clinical trials in the near future.

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