

# Clinical Outcome and Electrode Position Determined by the Fused Image of Preop MRI and Postop CT after Bilateral STN DBS

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**Purpose:** Many approaches have been utilized to precisely target the subthalamic nucleus (STN) in the bilateral STN stimulation for Parkinson's disease (PD). However, not all the patients have their electrodes positioned exactly in the STN after surgery. This study compared the surgical outcome with electrode positions confirmed at a stable period after bilateral STN DBS surgery.

**Material and Methods:** 57 advanced PD patients treated with bilateral STN DBS were enrolled in this study. Electrode positions were determined in the fused images of preoperative MRI and postoperative CT scans taken six months after surgery. The patients were divided into three groups: ① group I, both electrodes in the STN, ② group II, only one electrode in the STN, ③ group III, neither electrode in the STN. Unified Parkinson's Disease Rating Scale (UPDRS), Hoehn and Yahr Staging (H&Y), Schwab and England Activities of Daily Living (ADL), and levo-dopa equivalent daily dose (LEDD) were prospectively evaluated before and at 6 and 12 months after surgery according to the electrode positions.

**Results:** UPDRS, H&Y, and ADL scores significantly improved with a decreased LEDD at 6 and 12 months after bilateral STN DBS in the patients of both group I and II. The patients of group I had better outcome in speech especially when electrodes were located in the middle one third of both STN.

**Conclusion:** Electrode position in the middle one third of both STN leads to the best outcome including speech in the patients with advanced PD after bilateral STN DBS surgery.

**Key words:** Advanced Parkinson's Disease, Bilateral STN DBS, Clinical Outcome, Electrode Position: Fused Images, Preoperative MRI: Postoperative CT Scans

## Bilateral Deep Brain Stimulation of the Pedunculopontine Nucleus in Advanced Parkinson's Disease

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**Introduction:** Gait disturbance and postural instability are some the most disabling symptoms of idiopathic Parkinson's disease (PD) and in the late stage disease can be resistant to both medical and surgical therapies. The pedunculopontine nucleus (PPN) is thought to be involved in the initiation and modulation of gait and other stereotyped movements, because electrical stimulation and the application of neuroactive substances in the PPN can elicit locomotor activity in experimental animals. Recently it has been suggested that PPN could be a therapeutic target to improve gait in certain parkinsonian patients. Currently available therapies provide only variable degrees of control for axial signs of PD, such as in gait and posture. We report our first experience of clinical affects of DBS of PPN in a PD patient with severe axial signs such as gait and postural instability and discuss the pathophysiology of role of PPN.

**Methods:** A 72 year-old female patient with 12 years duration of PD selected had dominant symptoms of severe gait disturbance with intermittent freezing and postural instability in both the 'on' and 'off' states. She was assessed pre-operatively (H&Y stage 4) and post-operatively by applying the Unified Parkinson's Disease Rating Scale and time motor tests (on and off). Gait and balance dysfunction were also evaluated. After obtaining informed consent from patient and family, DBS leads were implanted bilaterally into the pedunculopontine nucleus under MRI-directed stereotactic technique and microelectrode recording. The target was calculated according to the Nieuwenhuys atlas, and Schaltenbrand and Wahren atlas. After operation, trial stimulation was given in lower stimulation frequency (10-20 Hz, 2-3 volts, 90 usec).

**Result:** We saw an improvement in gait, postural instability and other cardinal signs of PD in 'on' and 'off' state. She could not stand and walk for a while even in preoperative 'on' state. However, she could stand by herself in postoperative 3 days with external stimulation. She has become more stable in the pull test. Now she could walk with cane still with marked difficulty in balance though her gait and balancing difficulty has improved after operation. The dosage of medication did not change. No procedure-related complication or acute neurophysiological sequelae were found until postoperative 9 months.

**Conclusion:** We could see modest improvement in gait and balance with bilateral PPN DBS, however, these improvement was not as dramatic as expected. Considering the advanced stage of this particular patient, we thought that PPN DBS could be considered in certain patient with advanced PD with prominent balancing instability and gait disturbance.

# Thalamic Deep Brain Stimulation for Writer's Cramp

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**Objective:** Writer's cramp is a type of idiopathic focal hand dystonia characterized by muscle cramps that accompany execution of the writing task specifically. There has been renewed interest in neurosurgical procedures for the treatment of dystonia over the past several years. In particular, DBS has received increasing attention as a therapeutic option for patients with dystonia. The VO in the thalamus has been recognized as an appropriate target for radiofrequency ablation in patients with writer's cramp. In this report, we describe the clinical outcome of thalamic stimulation in patient who was treated for writer's cramp.

**Methods:** A 36-year-old female suffered from right hand tremor and dystonia aggravated especially during the writing task. She has been treated through drug medication for one year, but drug adverse effects made keep having medication difficult. Brain imaging study revealed no abnormal finding. Burke-Fahn-Marsden Dystonia Rating (BFMDR) scale was used to evaluate patients' pre- and post-operative neurological conditions. Her pre-operative BFMDR scale demonstrated 4 (unable to grasp to maintain a hold on a pen). We performed left thalamic deep brain stimulation for right focal hand dystonia. According to Schaltenbrand-Wahren atlas, MRI guided visual targeting and intra-operative microelectrode recording, we confirmed the accurate targeting point for ventral thalamic nucleus (VOA: nucleus ventrooralis anterior, VOP: nucleus ventrooralis posterior). After the implantation of DBS electrode (Medtronic, Inc.), we implanted a pulse generator at left subclavicular area.

**Results:** She improved neurologically after immediate post-operative period. Her post-operative BFMDR scale demonstrated 1 (slight difficulty in writing) compared with pre-operative BFMDR scale 4. Post-operative brain CT revealed the accurate electrode implantation for pre-operative targeting point.

**Conclusion:** Thalamic stimulation appears to represent an effective and safe therapeutic option. We report a successful case of thalamic deep brain stimulation for writer's cramp.

**Key words:** Writer's cramp, Deep brain stimulation, Ventral thalamic nucleus

## DBS Lead Anchoring: Skull Outer Table Drilling & Cap use Method

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**Objective:** To implant the DBS lead ,with consideration given to burr hole placement. Place a 14 mm diameter burr hole in the desired location.

For anchoring the lead, use the burr hole cap and ring packaged with the lead.

Usual anchoring method bulging the cap area showed. In the point of cosmetic view of the DBS operated women, it was not good.

**Material and methods:** I operated 60 DBS operations during last 5 years. 5 among them operated outer table drilling and burr hole cap stabilized.

**Result:** All five patients showed no elevated the burr hole cap site. Nobody complained operation site pain.

**Conclusion:** In the women or bald-headed person, skull outer table drilling and cap stabilization is very effective for DBS lead fixation.

**Key words:** DBS, Outer table, Burr hole

# Sacral Nerve Stimulation of Intractable Pain with Cauda Equina Syndrome

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**Objective:** Voiding and fecal dysfunction, which includes incontinence, retention, and chronic intractable pelvic pain, are relatively frequent problems in cauda equina syndrome that can be difficult to manage. Sacral nerve stimulation has been shown to improve these symptoms, although the exact mechanisms remain elusive. This report assessed the use of sacral nerve stimulation in the treatment of this condition.

**Material and methods:** The first of the 2 cases of cauda equina syndrome we report occurred following burst fracture of L1 after fall down. The second occurred after microdiscectomy of herniated lumbar disc 4-5 level. Fecal and urinary dysfunction and intractable pelvic pain were present in both cases. After various treatments failed, both patients were given sacral nerve stimulation of right S 3 level.

**Result:** A test stimulation of the S3 root was effective in both patients, and they were implanted successfully with a follow-up. Pain and accompanying bladder and bowel dysfunction of both patients were improved (VAS 5/9, 3/9) by temporary and permanent sacral nerve stimulation. So far no late failures have been seen.

**Conclusion:** We experienced 2 cases of cauda equina syndrome who were improved their pain and accompanying bladder and bowel dysfunction after sacral nerve stimulation. Sacral nerve stimulation is may be a useful option for intractable pelvic pain with cauda equina syndrome.

# Effectiveness of Spinal Cord Stimulation in Chronic Neuropathic Pain from Adhesive Arachnoiditis, a Particular Subtype of Failed Back Surgery Syndrome

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**Objective:** Spinal cord stimulation (SCS) is a direct clinical application of the gate theory initially proposed by Melzack and Wall and is gaining popularity as an effective means to control chronic neuropathic pain in complex regional pain syndrome (CRPS), failed back surgery syndrome (FBSS), and vascular ischemic pain, etc. Among them, failed back surgery syndrome is one of the most frequent indication of SCS. However, the term FBSS is composed of heterogeneous diseases such as missed spinal stenosis, foraminal stenosis, battered root syndrome, etc. among them, adhesive arachnoiditis has been known as a good indication of SCS. Authors report the effectiveness of SCS in a patient with chronic neuropathic pain of adhesive arachnoiditis and discuss the pathophysiology of adhesive arachnoiditis.

**Material and methods:** A 72 year-old man presented a chronic pain in his back and radiating pain to his buttock and posterolateral legs. On History, he underwent a laminectomy and tumor removal at L4/5 level in 1988 for his left buttock and leg pain. His old medical record was not available and it was thought as a kind of nerve sheath tumor. His pain improved after operation. After 5 years, he underwent an operation for L4/5 HNP for right leg pain which is the same level of previous tumor removal surgery. After operation, severe back and leg pain developed and this pain did not improved with maximal medical therapy and physiotherapy. At the time of referral, he suffered a chronic back and leg pain for more than 10 years. His back pain was continuous and back and leg pain aggravated with coughing and straining. His VAS was about 6-8/10. His pain did not responded to opioid and there was 2 attempts of suicides for chronic pain in history. After getting informed consent, a trial SCS was done. We explained him that his leg pain would respond to SCS but back pain is difficult to control with SCS, and the difficulty to control chronic neuropathic pain of adhesive arachnoiditis. His medication at the time of referral was; morphine 90 mg, oxycontin 40 mg, gabapentin 2,700 mg, tramadol 300 mg, acetaminophen 1,800 mg, with transdermal fentanyl patches.

**Results:** After inserting two percutaneous leads in the desired level according to the intraoperative stimulation mapping, the external stimulation was done for 5 days. His buttock and leg pain was relieved more than 70%, however his back pain was resistant to trial stimulation. The overall improvement was about 50% and the IPG was implanted in the right lower abdomen. After SCS, his opioid consumption reduced to oxycontin 20 mg, gabapentin 1800 mg, amitriptyline 20 mg, tramadol 150 mg. His VAS at 1year follow-up is about 4-5/10.

**Conclusion:** As shown in this particular patient, the chronic neuropathic pain of adhesive arachnoiditis responded to SCS. However, the coverage of back was difficult inspite of successful buttock coverage. For this condition, we think we could try another trial SCS in other level. The treatment of chronic pain of adhesive arachnoiditis is extremely difficult even with SCS, but the radiating nature of pain responded to SCS.

# Spinal Cord, Sacral Nerve Stimulation and Neurolysis for Misdiagnosed FBSS including Arachnoiditis Ossificans and Calcified Brachial Plexopathy

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**Objective:** We would like to introduce spinal cord and sacral nerves stimulation for the chronic intractable pain of misdiagnosed FBSS and neurolysis for ossificans arachnoiditis of lumbar and calcified brachial plexopathy.

**Material and methods:** ① diabetic peripheral neuropathy, which was misdiagnosed to FBSS, had thoracic spinal cord stimulation. ② CRPS type I developed after spine surgery for cervical cord injury had cervical cord stimulation 6month later. ③ Anal pain(proctalgia) which had operated with anterior spinal instrumentation and laminectomy for L2 fracture 7 years before had 4 pain-surgeries. At first the malpositioned anterior screw was removed, second bilateral sacral nerves (S3, 4) were stimulated, at third thoracic spinal cord from T 8 to L1 was stimulated during 10days and the last intradural adhesiolysis of rootlets with removal of the arachoiditis ossificans was done. ④ The calified fibrotic scar of brachial plexopathy was resected with neurolysis 5 months later. All cases had around 7 to 10 VAS score preoperatively.

**Result:** Diabetic polyneuropathy and CRPS type I improved after spinal cord stimulation. The brachial plexopathy has also satisfactory pain relief. Otherwise, the chronic anal pain during 7 years was still refractory.

**Conclusion:** We need to discriminate various pain modalities and causes from FBSS and brachial plexopathy as soon as possible.

**Key words:** Spinal cord stimulation (SCS), Sacral nerve stimulation, Arachnoiditis ossificans, Brachial plexopathy

# Exquisite Design of Stimulation Technique of SCS for Neuropathic Pain

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**Objective:** Spinal cord stimulation is widely used to control for intractable chronic pain due to various type of pain. Sometimes it is difficult to control the pain due to neuropathic pain. Author introduces recent experiences of a complex regional pain syndrome and a pain after cauda equina injury using spinal cord stimulation.

**Material and methods:** A patient with complex regional pain syndrome which developed due to multiple level of chronic herniated cervical disc showed a sharp, electrical shock like pain, and right arm weakness from C2-C6 with allodynia (VAS9-10). A 8 channel electorde and a 4 channel electrode were inserted into epidural space from C2 to C7. Trial stimulation showed the marked improvement of pain. So a stimulation generator was inserted. The other patient with unilateral leg pain due to incomplete cauda equina injury after L3 compression fracture complained severe tearing, electrical shock-like pain on right leg (VAS 9-10). Two 8 channel electrodes were inserted into epidural space from T8 to T12. Pain was improved during trial stimulation. So a stimulation generator was inserted.

## **Results and Conclusions:**

Postoperatively, the patient who had CRPS pain has been treated with 2 continuous mode and 6 cycle mode (frequency 28-40 Hz, pulse width 300-500 msec). His pain is markedly decreased, VAS is decreased from 10 to 5. The patient with cauda equina injury, has been treated with 2 continous mode and 2 cycle mode including dynamic multistimulation (frequency 28-32 Hz, pulse width 300-450 msec). His pain is markedly decreased, VAS is decreased from 10 to 4.

In conclusion, although it is difficult to control the pain due to neuropathic pain using SCS, a careful analysis of pain nature, a determination of stimulation sites and various modulation of stimulation parameters are very helpful to control pain.

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## Impact on Clinical Practice by the Perfexion Gamma Knife

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Two hundred and fifty patients have now been treated with the new Gamma Knife model Perfexion at the Cromwell Gamma Knife Centre in London. We recently compared the physical properties of the Perfexion with those of its predecessors. The distinctive properties of the new system include a larger reach of targets, increased versatility of shaping dose distribution around a single isocenter, more treatment time used for radiation and less for set up, more user friendly planning software, and more comfortable treatment conditions for the patient. These improved properties have enabled treatment of target volumes also below the foramen magnum, treatment of larger target volumes, steeper dose gradients and thus decreased exposure of eloquent structures, facilitated treatment of multiple isocenters, and increased work flow. The extended reach has widened indications to include skull base tumours extending into the upper cervical levels such as lower cranial nerve Schwannomas, Paragangliomas (glomus tumors), Adenoid Cystic Carcinomas a.o. Skull base tumors of volumes as large as 50 cc have been successfully treated. Facilitated shaping of individual isocenters and the fast transfer of the patient to a new treatment position (seconds) have made Gamma Knife surgery of large volumes and multiple targets such as multiple metastases practical. Coregistration of multiple imaging modalities has made treatment planning more accurate. Treatment follow has become easier by the facility of coregistering follow up images with treatment images.

## Invited Speakers

# Rationale for Treating Multiple Cerebral Metastases by Gamma Knife Surgery

**Christer Lindquist, M.D.**

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Whereas it is now generally accepted that radiosurgery in combination with WBRT improves results over WBRT alone there is no consensus on whether multiple metastases should be treated and if so in which patients. The general improvements of cancer treatment and the fact that even a large number of metastases can now be easily treated by the Gamma Knife has made resolution of these issues more urgent. Our recent experience from treatment of around 100 patients with an average of 6 brain metastases from breast cancer the survival time was on average around 1 year and as good as the reported survival for patients with single tumors. In many patients tumor relapse had occurred after WBRT which did not seem to have a significant impact on survival. On the other hand, control of systemic disease was strongly related to survival. In a cooperative retrospective study with 3 other Gamma Knife Centers of 1768 patients with cerebral secondary tumors from various forms of cancer the 5 years survival rate was 6% for all patients and 8% for patients with controlled primary disease. Diligent surveillance of treatment effects with follow up MRI and generous administration of repeated treatments have made an impact on patient survival and quality of life in patients with controlled sytemic disease.

# Unexpected Clinical Course after Gamma Knife Radiosurgery for the Intracranial Benign Lesions

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**Objective:** With increase of clinical experience of Gamma Knife radiosurgery for the Intracranial benign lesions, many informations about proper treatment indication and dose planning have been already known. However, we sometimes experienced the treatment failure or unexpected clinical course even in the cases with good radiosurgical indications.

Authors intended to introduce the interesting cases of unexpected clinical course after Gamma Knife radiosurgery for the intracranial benign lesions and discuss the presumptive causes.

**Methods:** Eleven cases, which showed increase of intracranial benign lesions after Gamma Knife radiosurgery during the follow-up period were selected in this study. Ten cases were benign brain tumors (acoustic schwannoma: 3 cases, trigeminal schwannoma: 2 cases, meningioma: 2 cases, facial schwannoma: 1 case, pituitary adenoma: 1 case) and one is pediatric cerebral AVM. We analyzed retrospectively the preoperative state of brain lesion, treatment planning data, and follow up results.

**Result:** Preoperative mean volume of lesions was 2.8 cc (0.3-5.5), which means the good radiosurgical indication in volume for treatment. In benign brain tumors, 12-15 Gy marginal doses were applied and 26.7 Gy of maximal dose and 20 Gy of marginal dose were in pediatric cerebral AVM. Mean follow up period was 40.6 (21-113) months, and mean duration from Gamma Knife radiosurgery to detection time of increase of intracranial benign lesions was 16.8 (10-39) months. Four cases needed the open surgery of mass removal, though their pathologic report revealed non specific finding. It was too difficult to explain the reason of unexpected clinical course by pathologic report of these cases. And second Gamma Knife radiosurgery was applied for another two benign brain tumor cases.

**Conclusion:** Most well known cause of treatment failure after Gamma Knife radiosurgery is dose-volume relationship. However, we could have the experience of treatment failure or unexpected clinical course even in case of good indication and proper treatment. Authors presumed that biologic factor or radiation-sensitivity in addition to low dose selection, target error would be closely related with unexpected clinical course after radiosurgery.

## Gamma Knife Surgery for Brain Metastases in Patients Harboring Ten or More Lesions

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**Objective:** The purpose of this study was to evaluate the outcome of gamma knife radiosurgery (GKS) in patients with a large number (ten or more) of metastatic brain lesions.

**Methods:** 26 patients were treated with GKS for ten or more metastatic brain lesions. The KPS score was 70 or more (that is RPA 1 or 2) in all patients. The primary tumor sites were the lung in 21 patients, breast in 3, and undetermined in 2. 20 patients were treated with whole brain radiotherapy before or after GKS and 6 patients were treated with GKS alone.

**Result:** A total of 432 lesions in 26 patients were treated initially, and 11 patients underwent repeated GKS more than once for recurrent lesions. The mean total target volume was 10.9 cm<sup>3</sup> (range 0.99-42.2 cm<sup>3</sup>). The mean marginal prescription dose was 16.5 Gy (range 9-23 Gy), and the median marginal isodose was 50% (range 50-70%). The overall median survival from the initial GKS was 27 weeks (range 8-287 weeks), and 44 weeks (range 10-287 weeks) from the diagnosis of brain metastases. Univariate and multivariate analyses revealed that higher KPS score and synchronous brain metastases were significant predictors for favorable survival. The tumor control rate at the last follow-up time was 66.5%. Of the 17 patients who were no longer alive at the conclusion of this study, 6 patients (35.3%) died of neurological causes.

**Conclusion:** GKS may be considered as an initial or salvage treatment option in patients with good performance (KPS score  $\geq 70$ ) even if they have a large number (ten or more) of lesions.

# Gamma Knife Radiosurgery for Intracranial Hemangioblastoma

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**Objective:** The authors retrospectively evaluated the outcomes after gamma knife radiosurgery (GKRS) for intracranial hemangioblastoma (HBL).

**Patients and Methods:** Between Dec 1997 and Dec 2006, thirty five patients with 95 HBLs underwent GKRS. Three patients (8.6%) were lost to follow-up, and 5 (14.3%) had follow-up less than 6 months. Therefore, we included 27 patients (16 men, 11 women; mean age 41.0 years; range 11.0-73.0) with 73 HBLs (mean volume 1.68 cm<sup>3</sup>; range 0.1-15.7) in this study. Eighteen patients (66.7%) had one lesion, and twelve patients (44%) with 58 HBLs (79.5%) were associated with von Hippel-Lindau (VHL) disease. The mean tumor marginal dose was 16.4 Gy (range, 11-22) and the mean shots was 3.7 (range, 1-18). The mean clinical and neuroimaging follow-up was 41 months (range, 3-116) after radiosurgery.

**Results:** At the last follow-up, 26 patients (96.3%) were alive and one patient (3.7%) with one lesion at near the medulla died from aspiration pneumonia 3 months after radiosurgery. Sixty nine (94.5%) among 73 tumors were controlled locally, so three tumors ultimately progressed in size 11, 41, and 98 months after radiosurgery, respectively. Six (22.2%) patients underwent additional surgical treatment after radiosurgery; two were operated on for tumor resection, two had diversion of CSF, one had drainage of tumor-related cyst, and one patient underwent repeated GKRS after ventriculoperitoneal shunt. Twenty three patients (85.2%) were neurologically improved or stable at the last follow-up. Tumor volume ( $p=0.002$ ), age ( $p=0.046$ ), and margin dose ( $p=0.047$ ) were factors affecting good outcome and tumor with cyst at the time of GKRS was negatively associated ( $p=0.002$ ) in univariate analyses. However, multivariate analyses indicated that smaller tumor volume was the most significant factor related with good outcome ( $p=0.002$ ).

**Conclusion:** Radiosurgery is an effective and safe treatment modality for especially small HBLs to control disease. However, HBL can re-grow at variable periods after radiosurgery, even after 8 years. And one should pay attention to complications, such as cyst enlargement and development of hydrocephalus after radiosurgery.

**Key words:** Hemangioblastoma, Radiosurgery, Gamma knife

## Gamma Knife Radiosurgery for Multiple Brain Metastases from Lung Cancer

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**Objective:** The aim of this study was to compare the effectiveness of gamma knife radiosurgery (GKS) for multiple brain metastases from lung cancer with that of whole brain radiation therapy (WBRT).

**Methods:** Patients with multiple (from 2 to 20) brain metastases were divided into a GKS group (14 patients) and a WBRT group (19 patients) for initial brain tumor management. The overall and qualitative survival was calculated using the Kaplan-Meier method. Patients were stratified by gender, age, pathological type of lung cancer, initial Karnofsky performance status (KPS) score, control of primary site, known extracranial metastases, number of brain metastases, diameter of the maximal lesion, chemotherapy, and recursive partitioning analysis (RPA) Class. Results: The 6-month and 1-year survival rates were 64.3% and 47.7% in the GKS group and 42.1% and 10.5% in the WBRT group for overall survival. The median survival time was 32 weeks in the GKS group and 24 weeks in the WBRT group. The overall survival time in the GKS group was significantly longer than in the WBRT group ( $p=0.0426$ ). The qualitative survival was significantly longer in the GSK group ( $p=0.0174$ ). The survival was improved in patients with a controlled primary tumor site by univariate and multivariate analysis ( $p=0.032$ ,  $0.019$ ).

**Conclusion:** GKS for patients with multiple brain metastases significantly improved patient survival compared with WBRT. When we assessed subgroups, systemic disease control was the only significant variable in the multivariate analysis.

**Key words:** Brain metastasis, Gamma knife surgery, Whole brain radiation therapy, Lung cancer

# Novalis Stereotactic Radiosurgery for Cranial and Spinal Chordoma

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**Objective:** Chordomas are slow-growing and locally invasive tumors that occur at the neural axis of cranial base and spine. Adjuvant radiation has become a mainstay in the treatment of chordomas. A combined surgery and irradiation affords the patient disease-progression free survival. Although chordomas were once considered radioresistant tumors, improving radiosurgical technology has allowed more conformal and escalated radiation dose to the tumor beds.

**Patients and Methods:** Since Feb. 2001, a total of 16 patients with 4 clival and 12 spinal chordomas were treated using fractionated stereotactic Novalis Radiosurgery. The ratio of male to female was 14:2. Mean age was 49 years. Median radiation dose was 18 Gy of single equivalent dose. Median follow up period was 6 months (ranged from 3 to 84 months).

**Results:** 11 patients who received more than 18Gy of radiation dose had clinical improvement remained stable and local tumor control. Two patients showed recurrent lesions and required repeat surgery and/or radiosurgery. One patient was lost to follow-up. Ongoing follow up is necessary for remaining two patients.

**Conclusion:** Intensity modulated and fractionated Radiosurgery using Novalis system can offer to deliver an effectively high radiation dose into the tumors with less collateral radiation damage to the adjacent critical normal tissues.

# Neuromodulation: Where Will We Be in the Next Few Years?

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For over 50 years, deep brain stimulation (DBS) has been used to treat refractory chronic pain-with mixed results. Over the last 20 years, however, DBS has become a well-established treatment for many movement disorders, including Parkinson's disease. More recently, DBS has been in trials for refractory epilepsy, headache, and mood disorders (notably severe depression and obsessive-compulsive disorder).

This report will focus on these new indications for DBS, with emphasis on the new techniques and technologies which are under development. Two main themes are likely to advance DBS significantly in the next 5 to 10 years:

- Closed-loop DBS, i.e. feedback from brain electrical activity to direct the stimulation
- Computational analysis, which includes both visual/anatomic as well as electrophysiological modeling of the brain to enhance DBS

With regard to closed loop DBS, the most advanced application currently is in epilepsy. Work supporting the application of closed-loop (feedback) DBS for epilepsy is reviewed, and the technique of 'responsive neurostimulation'(RNS) is summarized.

With regard to computational analysis for DBS, the most immediate techniques-presently available for clinical use in some instances-are sophisticated imaging techniques which include on-lays upon a 3-D MRI of the brain of (1) nerve fiber tracts (diffusion tensor imaging), and (2) volume of tissue activated by a specific electrode.

Research is rapidly progressing on novel techniques for DBS beyond the use of feedback loops and enhanced imaging. These include the use of mathematical models of brain electrical activity to model the abnormally-synchronized electrical activity which is the hallmark of epilepsy and many movement disorders, including Parkinson's disease. By incorporating feedback loops and multiple recording and/or stimulating sites in the brain (the specific sites depending upon which disorder is being treated), the abnormally-synchronized brain electrical activity can not only be desynchronized, but may be 'unlearned'-'unkindling' in the example of epilepsy. Characteristics of this type of DBS include:

- The use of low-frequency stimulation rather than high-frequency stimulation
- The need for multiple stimulation and/or recording sites
- The marked reduction in electrical current needs (likely 10-fold or more), which will permit much smaller 'pulse generators'
- Fewer unwanted side effects of stimulation due to more focused and less disruptive stimulation techniques
- The potential to 'cure' certain disorders by resetting the abnormal firing patterns back to normal

However, with these advantages of more sophisticated DBS techniques come the following challenges-challenges that are likely to require a decade or more of research before they become techniques in clinical practice:



- Since many brain disorders involve neurotransmitter abnormalities (in levels or in distribution throughout the brain, e.g. dopamine in Parkinson's disease), how do we monitor and modulate neurotransmitters in a manner similar to monitoring and modulating electrical activity?
- How do we get multiple microelectrodes into the brain in a minimally-invasive manner?

In the second report, we address these two issues and offer some potential solutions.

## Neuromodulation: Where We Might Be in the Next Few Decades!

**Russell J. Andrews, M.D.**

*Ames Associate Smart Systems & Nanotechnology, NASA Ames Research Center, Moffett Field, CA, USA*

Several indications for DBS-notably Parkinson's disease and mood disorders - appear to be disorders of neurotransmitters more than disorders of brain electrical activity. Indeed, a major difficulty with pharmacologic treatment for such disorders is the inability to target the treatment drug to the precise location(s) in the brain where the neurotransmitter imbalances occur - the drug spreads throughout the central nervous system (CNS) in most situations. Along the same line, data are accumulating that non-neuronal cells in the CNS - notably astrocytes - play a crucial role in neuronal activity (through both electrical and neurochemical modulation of nearby neurons). Perhaps the term 'neuromodulation' should be substituted for DBS as we include brain neurochemistry along with brain electrical activity in our therapeutic armamentarium.

With regard to neurotransmitter monitoring, carbon-fiber microelectrodes (as small as 5  $\mu\text{m}$  diameter) and fast-scan cyclic voltammetry have been used in freely moving small animals to monitor levels of neurotransmitters such as dopamine with a response time of 0.1 sec. For example, it has recently been shown that dopamine release is heterogeneous within various regions in the rat nucleus accumbens - a finding likely to be important as we move toward neuromodulation for mood disorders.

As we become more sophisticated in functional localization in the brain, it is clear that more precise monitoring (both electrical and neurochemical) and modulating/stimulating (again, both electrical and neurochemical) will be essential for optimal therapeutic benefit in specific disorders and specific patients. It is likely we may want to monitor/modulate axons or cell bodies - or even intracellularly - in a selective manner. Since neuronal cell bodies are on the order of several microns in diameter, and axons/dendrites smaller still (not to mention the size of the synaptic cleft), the ability to fabricate ultramicroelectrodes for neuromodulation is of paramount importance - first in the animal research setting, but eventually in clinical practice as well.

The work at NASA Ames Research Center and elsewhere on nanoelectrode arrays for neuromodulation is summarized. To date, nanoelectrode arrays have been fabricated and processed (coated with polymers, nerve growth factors, etc) to support neural networks of PC12 cells (neuron-like cells that can secrete dopamine under certain

## Invited Speakers

conditions). The capability of monitoring both electrical activity and neurotransmitter levels with improvements in spatial and temporal resolution far beyond conventional microelectrodes has been demonstrated. The next step is comparing the efficacy of nanoelectrode arrays (in microelectrode configuration) with conventional microelectrodes in established animal models of epilepsy and Parkinson's disease. Following this comes the reduction in size of the nanoelectrode arrays to allow precise monitoring/modulating (electrically and neurochemically) at the subnucleus if not the individual neuron level - in the dispersed manner that the computational models indicate will be much more effective at desynchronizing the abnormally-synchronized firing patterns of, e.g. epilepsy and Parkinson's disease.

But what about getting all these micro- or nano-sized electrodes into the brain non-invasively? We here rely on the dramatic advances of our interventional neuroradiology colleagues. Proof-of-principle has been demonstrated that ultramicroelectrodes (500 nm diameter) can be advanced into capillaries and used to stimulate CNS tissue with a response virtually identical to extra-capillary microelectrodes. It is not unreasonable to expect that in the next 10 to 20 years we will be able to place hundreds if not thousands of sub-micron-sized monitoring/modulating electrodes wherever needed in the brain.

The coming decades in the 21<sup>st</sup> century will be a very exciting time for functional neurosurgery!

## Different Firing Patterns with Burst Activities in Lateral Thalamic Nuclei

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김종현 · F. Lenz, 박정울 · 박윤관 · 정흥섭 · 정용구

**Objective:** It had been suggested that low threshold calcium spike (LTS) related bursting activities are limited to sleeping states or certain pathological conditions, but its possible relation to attention in awakened states has been repeatedly reported. We tested if there are different firing patterns of bursting activities from lateral thalamic nuclei and if the pattern is changing over prolonged awakened states.

**Materials and Methods:** A total of 117 lateral thalamic cells from 26 essential tremor patients were evaluated. For evaluation of long lasting changes of spontaneous bursting activity in awakened states, patients were asked for serial counting task for the periods about 30 to 60 seconds intermittently. Isolated spontaneous neuronal activities were then digitized at 50 kHz and stored on PC for the postoperative analysis. After sorting the digitized spikes, burst detection was done by using 50-6-16 ms criteria. Patterns of spike trains were evaluated by using 2 dimensional ISI plots with logarithmic scales and classified as grouping, non-grouping and intermediate states. Each pattern was compared to each other by parameters like firing rates and burst indexes like burst rates, mean preburst-intervals and burst percentages.

**Results:** A total of 29 cells were classified as grouping cells, 64 cells as non-grouping and 24 cells as intermediates cells. Each group showed significant differences in various parameters. The group classified as grouping cells showed lower firing rates with higher burst rates and non-grouping cells showed higher firing rates with lower burst rates. Each group showed stable patterns of activities even over several minutes.

**Conclusion:** These results suggest that there are different firing patterns with burst activities in lateral thalamic nuclei and it can be stable over prolonged periods in awakened states.

## Hardware-related Complications of Deep Brain Stimulation: Implant Erosion in Scalp

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At each step of a deep brain stimulation(DBS) procedure, hardware-related complications may occur and will have to be managed or avoided. This study evaluated the scalp erosion and/or infection in hardware-related complications of deep brain stimulation.

From March 2006 through February 2008, Four of 56 patients with 106 DBS procedures in our hospital developed scalp erosion over implants. The mean follow-up period was 12 months. Two patients with scalp erosion had diabetes. We also handled scalp erosion in two patients who underwent DBS at other hospital. Erosion location in scalp occurred at the burr hole site (n=1) or the connector site (n=3), or both (n=2). The procedure were performed to debride infected wound (n=1), remove hardware (n=2), replace infected device (n=2). They had a linear skin incision and the Medtronic fixation device at the burr hole site. In five patients with skin erosion over the connector site, their connector was placed on the parietal bone in 4 cases and on the retromastoid bone in 1 case. We have recently handled anchoring of DBS electrodes using a microplate following a curvilinear skin incision and drilled a trough in the cranial surface for securing the connector.

Scalp erosion may be associated with differences in the method for skin incision, electrode fixation at burr hole site and securing of connector. Attention to such details may decrease the risk of complications. We also will discuss a surgical method associated with implantation of DBS systems with regard to skin incision, electrode fixation and securing of connector.

# Effects of Subthalamic Nucleus Deep Brain Stimulation on Parkinsonian Resting Tremor: An MEG Study

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**Objective:** The pathophysiological mechanisms of Parkinsonian tremor is still not fully understood. We have studied the MEG and EMG signals of the upper limbs during resting state and isometric motor contraction with hands from Parkinsonian patients who underwent bilateral STN DBS surgery. We compared the EMG and MEG oscillatory patterns when the DBS was 'On' and 'Off' respectively, during the above states. We calculated the coherence between M1 and EMG to find the relationship between the two.

**Method:** Whole scalp MEG data and EMG signals were obtained from Parkinson's disease patients in both DBS 'On' and 'Off' states. Coherence was calculated in the frequency band of 1-30 Hz. EMG raw data were studied also.

**Results:** M1-EMG coherence in the rolandic area is prominent around tremor frequency and its harmonics when DBS is 'Off' for resting state data. Coherence tends to diminish when the DBS is 'On'. Raw data shows that regular tremor still exists when DBS is 'On', though the amplitude is significantly decreased.

**Conclusions:** Tremor apparently diminishes when the DBS is 'Off'. Since the coherence tends to flatten when the DBS is 'On', we may speculate that the stimulation on the subthalamic nucleus effects the synchrony between M1 and EMG data of the contralateral limb, resulting in a reduced EMG amplitude, or power. This may be related to the diminished Parkinsonian tremor, but much intensive investigation must be applied in the future.

## Thalamic Deep Brain Stimulation Combined with Bilateral Cingulotomy for Post-stroke Pain

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Pain is the common complaint of patients seeking medical attention. But, some patients fail to achieve adequate relief and side-effects arise with high doses of medication. Neurosurgical approach for the relief of pain is increased gradually, deep brain stimulation(DBS) is known to be an effective method of intractable chronic pain and cingulotomy has also been advocated for the management of pain. The authors suggest a new method for controlling of neuropathic pain. We performed DBS and cingulotomy simultaneously for three patients. The first patient was a 47-year-old female who had presented with neuropathic pain on left hemi-body due to previous intracerebral hemorrhage. She had underwent medication, acupuncture and other non-surgical pain relief procedure but has no effect. The second patient was a 47-year-old male, and had an operation history due to removal of intracerebral hemorrhage. He also had been treated for several years with multiple analgesics but pain was persistent. The third, a 55-year-old female, suffered from left-side foot and hand pain after intracerebral hemorrhage. The authors performed sensory thalamic nucleus stimulation and bilateral cingulotomy for patients, and good relief of the pain was achieved just after the operation. The result was measured with visual analogue scale (VAS) score. The VAS score reduced from 9 to 2 in a first patient, from 7 to 3 in a second patient, from 8 to 2 in a third patient.

We describe our surgical results of 3 patients of neuropathic pain treated with sensory thalamic DBS and cingulotomy with good result and expect this procedure may play a role in the treatment of the neuropathic pain.

# Effect of Temporal Lobe Epilepsy on Kanguage Pathway: Analysis with Diffusion Tensor Imaging Focused on Uncinate and Arcuate Fasciculus

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**Objective:** Seizure activity can change property of gray and white matter in seizure network and this may be identified with diffusion tensor image. Language pathway is composed of ventral and dorsal systems. The arcuate fasciculus (AF) and uncinate fasciculus (UF) are well known language pathway of dorsal and ventral pathway. Those tracts also can be included in seizure network. The purpose of this study is to analyze the effect of temporal lobe epilepsy to language pathway and to analyze different effect on those pathways.

**Material and method:** Thirteen left medial temporal lobe epilepsy (mTLE) and 12 right mTLE patients were enrolled in this study. All patients have language function on left hemisphere in Wada test. Ten neurologically healthy controls were also enrolled. Diffusion tensor image (DTI) was obtained in all of patients and DTIstudio program (Johns Hopkins University, Baltimore, USA, [www.mristudio.org](http://www.mristudio.org)) was used for individual tractographic analysis. The mean fractional anisotropy (FA) and apparent diffusion coefficient (ADC) were measured for individual tract. FA ratio and lateralization index of FA including those factors were compared within group and between groups.

**Result:** Intragroup comparison according to sidedness was performed first. Left mTLE group showed more decreased mean FA of left UF ( $p=0.032$ ). Right mTLE group showed more decreased mean FA of both right UF and AF ( $p=0.005$  and  $0.023$ ). The FA change of UF is more prominent than AF in left mTLE group ( $p=0.023$ ) and right mTLE group ( $p=0.039$ ).

Intergroup analysis was performed thereafter. Bilateral AF and UF showed decreased fractional anisotropy (FA) value comparing control ( $p<0.05$ ) in both left and right mTLE groups. The mean FA value of left UF was more decreased in left mTLE group than right mTLE group ( $p=0.031$ ). The relative ratio of FA of UF was decreased in ipsilateral to lesion side and increased in contralateral to lesion side ( $p=0.01$ ).

**Conclusion:** The medial temporal lobe epilepsy affects bilateral uncinate fasciculus and arcuate fasciculus. The uncinate fasciculus is affected more than arcuate fasciculus in both left and right mTLE. Left uncinate fasciculus is more affected by left mTLE than right mTLE and this may decrease function of ventral system. Increased ratio of FA may show brain plasticity of uncinate fasciculus, although the correlation of fractional anisotropy and function of tract has not been revealed, yet. More study with the result of neurophysiologic test should be followed.

## Update on Human Brain Mapping

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### 장 종 희

뇌교종의 수술의 목적은 수술로 인한 신경학적 장애 및 수술의 위험도를 최소화하면서 종양을 최대한 절제하여 adjuvant therapy의 효과를 극대화시키는 것이다. 하지만, 많은 경우에서 병변이 eloquent area에 위치하거나 근접해 있고, 개인간 anatomofunctional variability가 많아, 각각의 환자에서 cortical functional organization, effective connectivity and potential for plasticity를 확인해야 한다.

또한, 최근 수술 전 functional neuroimaging, 수술 중 해부학적 mapping tools (functional navigation system, 5-ALA, and intraoperative imaging), 그리고 수술 중 기능적 mapping tools (SSEP, MEP, awake 마취나 전신마취 하에서의 direct cortical or subcortical simulation) 등의 발전에 따라 정확하고, 안전하게 중요 구조물을 확인하면서 수술을 할 수 있게 되었다. 즉, 수술적 절제 전에 각 환자에서 cortical functional organization을 파악하고, 병변이 침범한 부위에서 주변 조직과의 관계 및 양상, 병변을 제거하면서 subcortical stimulation을 통해 anatomofunctional connectivity, 반복적인 수술 중 전기자극을 통해 short-term plasticity 등을 확인하여, eloquent area에 위치한 병변 절제 정도를 tailoring 할 수 있게 되었다.

또한, 수술적 기법의 발달과 더불어 eloquent area에 대한 해부학적, 신경생리학적 이해가 향상되고, 새로운 지식이 많이 보고됨에 따라 수술 성적을 크게 향상시키는데 기여하고 있다.

이러한 eloquent area에 대한 기본적인 지식, 이 부위 병변에 대한 수술을 통한 brain mapping 경험이 쌓이면서 뇌의 dynamic functional anatomy를 보다 잘 이해할 수 있게 될 것으로 본다.



# 중추신경계 질환에서의 간엽줄기세포 치료 연구

가톨릭대학교 의과대학 신경외과학교실

전 신 수

## I. 서 론

줄기세포의 이용으로 난치병을 치료하고자 하는 노력은 21세기 생명과학계의 중요한 이슈로 부각되고 있다. 심혈관계, 신경계, 혈액 및 면역계, 유전병, 간질환, 내분비 질환, 골, 연골, 피부 질환 등 거의 모든 영역에서 변화를 일으키고 있으며, 특히 과거 의학적 한계로 여겨졌던 퇴행성 질환이나, 말기 장기부전 등의 특별한 치료 방법이 없는 질환에 대해서 줄기세포를 통한 재생의학이 새로운 장을 열어가고 있으며, 암 질환에 있어서도 줄기세포를 유전자 전달체로 이용하는 유전자 치료에 대한 연구가 활발히 진행 중이다<sup>1,2</sup>.

중추신경계 질환이란 중추신경계를 구성하는 신경세포의 영구적 파괴 또는 기능장애에 의해 초래되는 질병을 말하며, 심각한 사회문제임에도 불구하고 뇌신경 조직은 손상 시 이를 복구할 수 있는 능력이 매우 제한적이어서 아직까지 뇌신경 질환에 대한 근본적인 치료법이 개발되어 있지 않다<sup>3</sup>. 또한 악성 뇌종양은 일반적으로 수술적 제거 후 항암제투여 및 방사선 치료 등의 복합적인 방법으로 치료하려 하고 있지만, 그 결과가 만족스럽지 못하며, 또한 이런 기본적인 치료를 다 시행해도 예후를 뚜렷하게 좋게 하지는 못하고 있는 실정이므로 새로운 치료 방법이 절실히 요구되는 상황이다<sup>4</sup>.

줄기세포는 크게 두 가지로 구분되어 지는데, 발생 초기의 배반포(blastocyst)에서 얻어지는 배아줄기세포와 발생 과정이 끝난 태반 또는 성인에서 얻어지는 성체줄기세포가 있다. 두 종류 각기 다른 특성과 장단점을 가지고 있으나, 현재 임상학적인 측면에서 골수나 제대혈 및 지방세포에서 쉽게 얻을 수 있는 성체줄기세포인 간엽줄기세포(mesenchymal stem cell)가 자가 재생능력, 다양한 세포나 조직으로 분화할 수 있는 능력, 병소부위로 찾아갈 수 있는 능력(tropism)이 있어 전 세계적으로 활발히 연구가 진행되고 있다<sup>5</sup>.

본 강좌에서는 현재 줄기세포 치료의 연구 동향과 더불어, 간엽줄기세포의 신경세포분화에 대한 연구와 간엽줄기세포를 이용한 척수손상, 뇌졸중 및 악성 뇌종양 치료에 대한 본 연구실의 연구 결과를 소개하고자 한다.

## II. 본 론

### 1. 간엽줄기세포의 특성 및 신경세포분화 연구

줄기세포란 조직을 구성하는 각 세포로 분화되기 전단계의 미분화 세포들을 총칭하며, 특정 분화 자극과 환경에 의해 특정 세포로 분화가 진행된다. 세포분열이 정지된 일반 세포와는 달리 세포분열에 의해 자신과 동일한 세포를 생산할 수 있는 특성(self-renewal)을 가지고 있고, 분화 자극에 의해 여러 다른 세포로도 분화될 수 있는 유연성(plasticity)을 가지고 있는 것이 특징이다<sup>6</sup>.

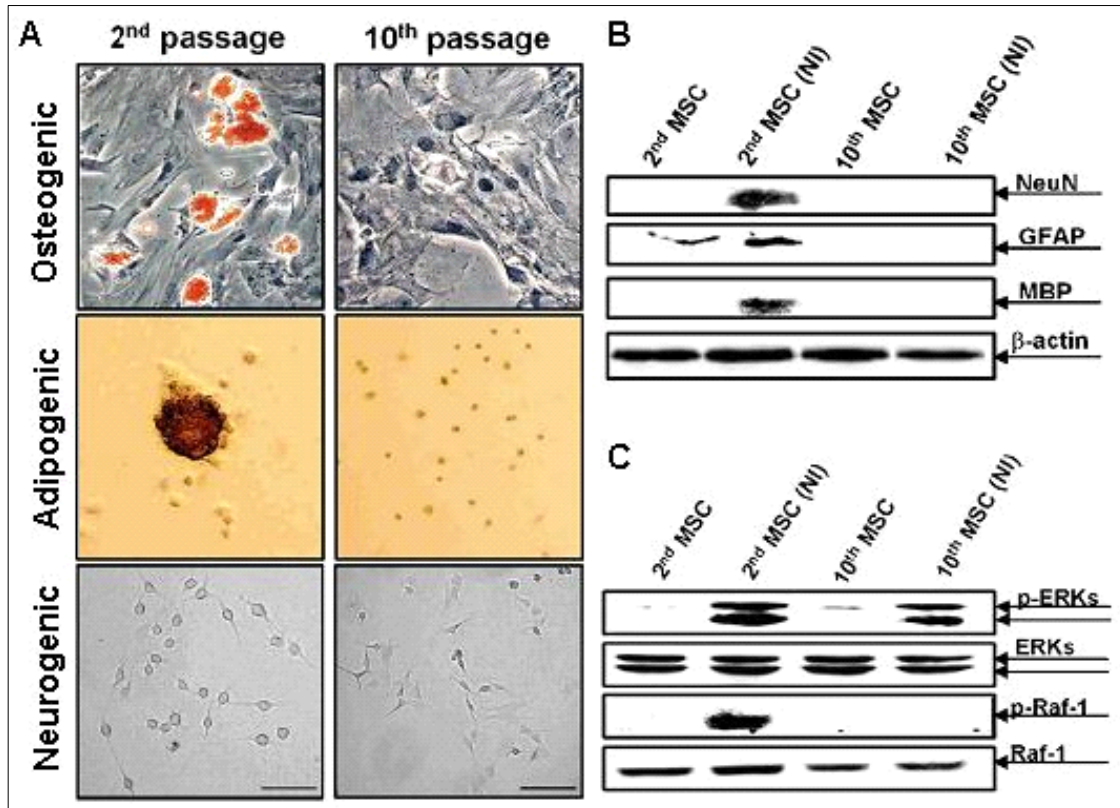
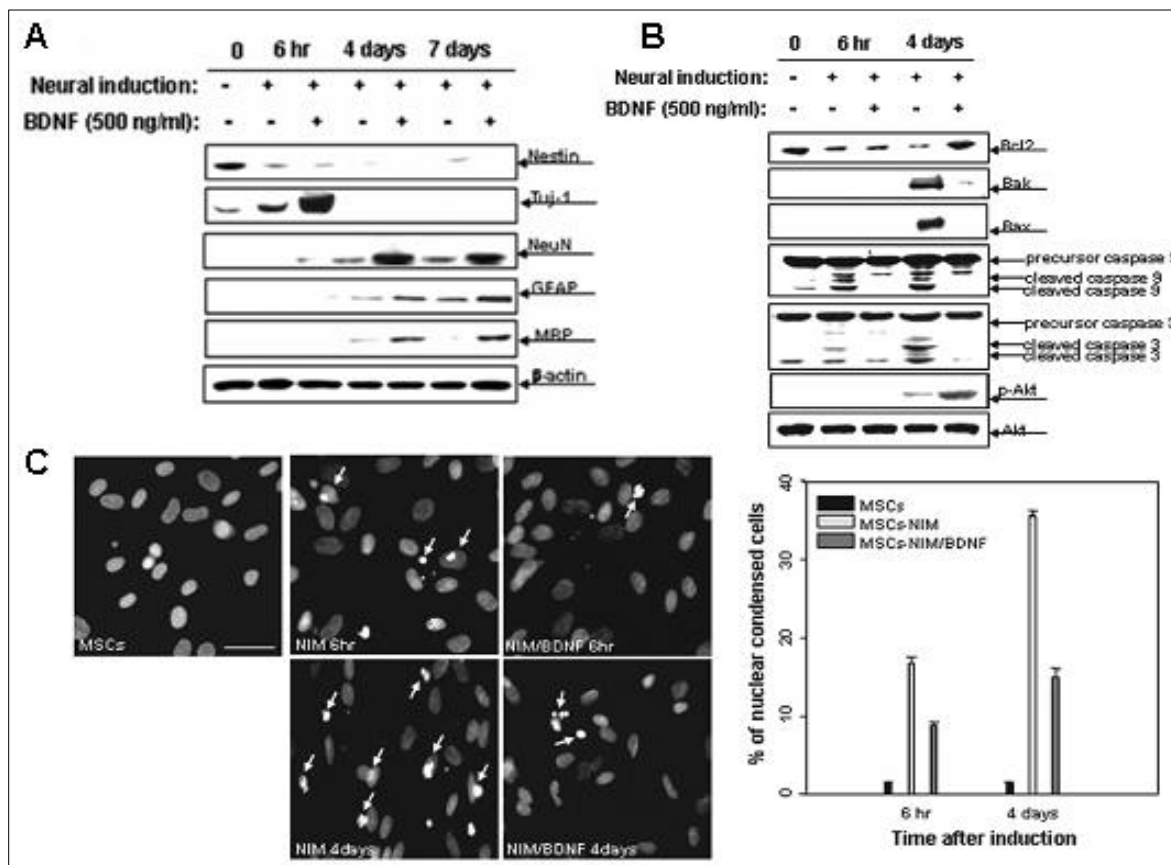


Fig. 1. Multiple stem cell traits of expanded rat bone marrow stromal cells (BMSC). Osteogenic, adipogenic, and neurogenic differentiation (A), expression of neuron-specific markers (B), and expression of neural-differentiation-related genes (C) in the neural-induced 2nd passage and 10<sup>th</sup> passage BMSC.

본 연구진은 쥐의 골수유래 줄기세포(bone marrow stromal cells)의 다중 분화능(osteogenic, adipogenic, and neurogenic)을 확인하였으며, 특히 신경세포로의 분화 능력은 세포의 passage가 지날수록 점점 감소하는 것을 알 수 있었다. 그리고 이러한 분화조건에서 신경세포 특이 단백질(NeuN, GFAP, and MBP)의 발현과 신경세포 분화에 관련된 단백질(p-ERK and p-Raf1)의 발현도 passage에 따라 감소한다는 것을 증명하였다<sup>7</sup>(Fig. 1).

최근 제대혈 내에 혈액과 면역체계를 만들어 내는 줄기세포인 조혈모세포(hematopoietic stem cell)와 다양한 간엽세포 및 신경세포로 분화가 가능한 간엽줄기세포가 들어있다는 것이 밝혀지면서 세포치료에 제대혈을 이용한 연구가 활발히 이루어지고 있다. 제대혈은 어른의 골수보다 더 미성숙하여 이식편대숙주병(graft vs. host disease) 발생이 적다는 장점으로 각광받게 되었다. 또한 산모나 태아에 영향을 주지 않으면서 쉽게 얻을 수 있고, 골수나 말초혈액에 비해 바이러스 감염의 빈도가 낮으며, 냉동 보관하였다가 필요시 즉시 공급할 수 있다는 장점이 있다<sup>8</sup>. 제대혈유래 간엽줄기세포는 골수에서 얻은 간엽줄기세포와 같이 다양한 분화 조건에서 배양하면 골아세포, 연골세포, 근세포, 지방세포 및 신경세포 등으로 분화가 가능하다는 것이 밝혀졌고<sup>9</sup>, 이 세포를 동물의 질병이나 손상된 부위에 이식시킴으로써 해당 질병을 치료할 수 있는 가능성을 제시하고 있는 연구 결과들이 많이 보고되고 있다.

본 연구진은 제대혈유래 간엽줄기세포(umbilical cord blood-derived mesenchymal stem cells)의 분화에 관한 연구에서 신경영양성장인자 중 Brain-derived neurotrophic factor (BDNF)가 신경 세포로의 분화 및 세포 증식



**Fig. 2.** BDNF enhances the neural differentiation of umbilical cord blood-derived mesenchymal stem cells (MSCs) and protects the differentiated neuron-like cells from the apoptosis. (A) Expression of neural markers in presumptive neurons derived from MSCs. Western blot analysis (B) and apoptosis was estimated by the nuclear condensation assay (C) carried out on MSCs before and after 6 hr and 4 days of incubation in neural induction medium (NIM) with or without BDNF.

에 미치는 영향을 조사하였다. 신경 세포로 분화시키는 조건 배지에 BDNF를 첨가한 결과, BDNF가 첨가된 분화 유도 조건의 간엽줄기세포에서 그렇지 않은 세포보다 신경 세포의 마커(Tuj1, NeuN, GFAP, and MBP)의 발현이 증가되는 것으로 보아 신경 세포로 분화가 더 잘 되는 것을 알 수 있었고, anti-apoptotic 단백질 발현의 증가와 더불어 caspase pathway를 저해하여 일반 조건 배지의 세포보다 증식능력 면에서 더 좋은 것으로 나타났다<sup>10</sup>(Fig. 2).

## 2. 중추신경계 질환에서의 간엽줄기세포 치료 연구

중추신경계는 생체 조직 중 가장 분화가 잘 된 조직으로 성체에서 손상을 받아 신경세포의 소실이 발생할 경우 신경망이 파괴되어 이에 따른 신경계의 기능부전이 발생할 뿐만 아니라, 손상된 신경은 재생이 불가능하여 비가역적 기능 소실은 영구적인 것으로 알려져 있다.

세포 이식 치료를 통해 우리가 얻고자 하는 치료 효과는 크게 세 가지로 나눌 수 있다<sup>11</sup>. 첫 번째로는 세포를 병변부위에 직접 이식하여 결핍된 세포를 대체해 줌으로써 특정 세포 결핍으로 인한 기능 소실을 복구하는

## 특 강

것이며, 두 번째로는 줄기세포가 가진 가소성(plasticity)이라는 특징을 이용하는 것으로서 이식된 주변의 환경에 따라서 세포가 이동, 조절되어서 원하는 세포로의 분화가 가능하기 때문에 뇌질환의 기능적, 형질적 회복을 기대해 볼 수 있으며, 세 번째로는 성체 신경줄기세포의 존재가 밝혀지면서 뇌신경조직에 존재하는 신경줄기세포를 자극하여 병변 부위로 이동, 증식 및 신경 세포로의 분화를 유도하는 전략으로서 세포 치료의 문제점인 공급, 윤리적 문제, 이식 세포의 면역거부 반응에 따른 세포 사멸 등의 문제가 없는 보다 근본적인 방법이라 할 수 있으나, 이를 위해서는 신경줄기세포의 이동, 증식, 분화기전에 관한 정보의 축적이 요구된다.

이제까지 난치성 중추신경계 질환의 치료는 약제나 효소 등을 전신적으로 투여하여 왔는데, 결핍된 neurotransmitter를 보충해 주는 수준이었고, 또한 뇌-혈관-장벽(blood-brain-barrier)으로 인해 원하는 곳까지의 운반의 한계점을 보였다. 최근 다양한 바이러스 매개체를 이용하여 유전자 치료를 시도하고 있으나, 광범위한 병소에는 적용되지 못하며, 이미 손상된 신경세포 및 회로를 재건하는 데는 한계점을 보인다. 이러한 난치성 신경계 질환의 새로운 치료로 줄기세포 치료에 대한 연구가 활발히 이루어지면서 손상되어 없어져 버린 세포를 대체하여 궁극적으로 신경회로가 재건될 수 있다는 가능성으로 치료적 유용성에 대한 관심이 증대하고 있다.

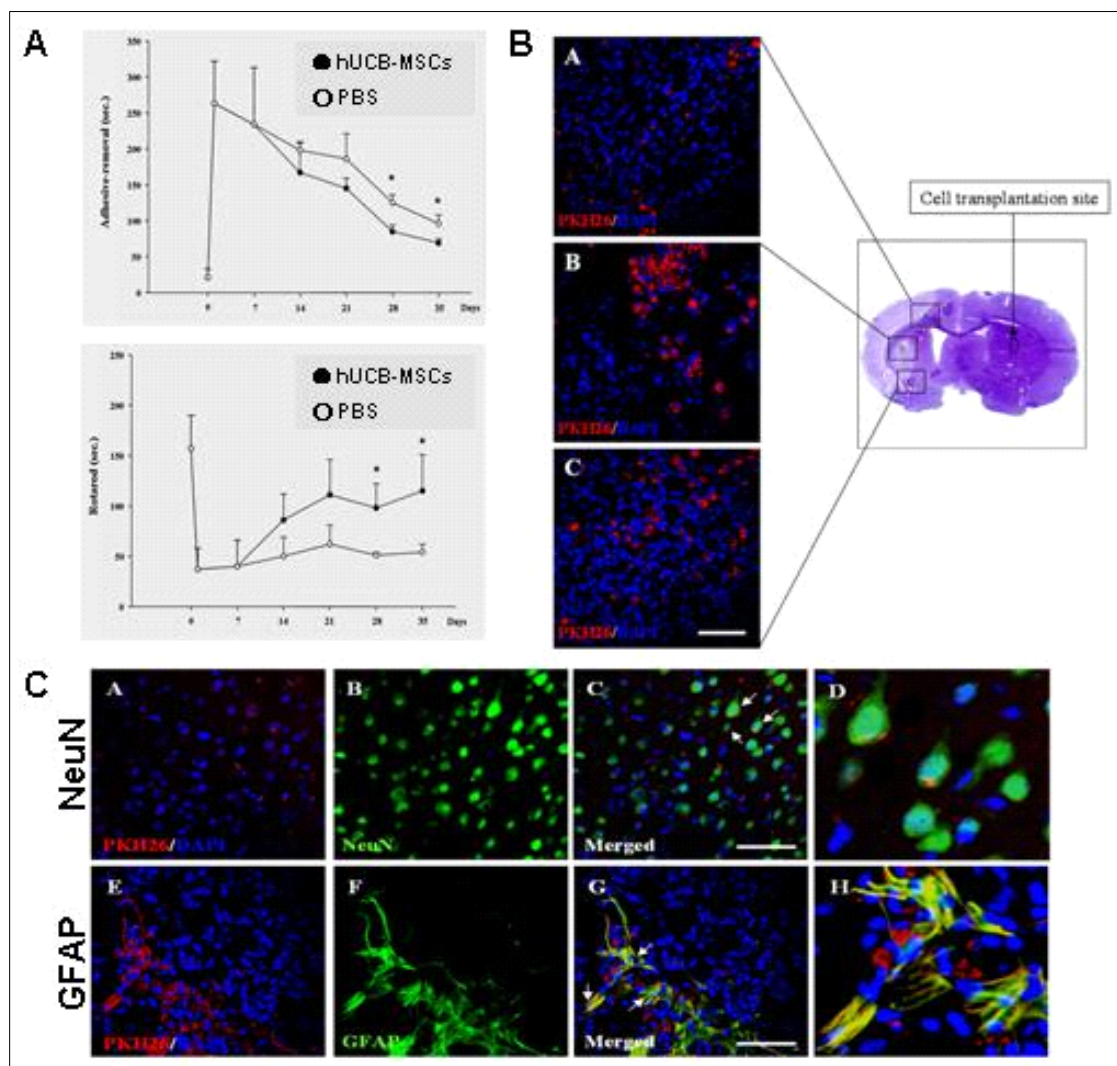
최근 골수의 간엽줄기세포가 신경계 세포로 분화할 수 있다는 것이 밝혀지면서 척수손상과 뇌졸중 동물모델에서의 연구 결과들이 많이 보고되고 있다. 간엽줄기세포를 손상 받은 척수 부위에 이식하면 이들 세포들이 손상부위를 연결하는 교량역할을 하고 여기에 GFAP 또는 neurofilament 양성인 신경세포들이 침투하여 기능적 회복을 유도한다는 보고가 있다<sup>12</sup>. 또한 뇌졸중 동물모델에서도 골수의 간엽줄기세포를 BrdU에 염색한 후 이식하였을 때, 전체 염색된 세포의 약 20% 정도가 허혈성 손상을 받은 뇌 조직에 침투하며, 이 중 약 5% 가량의 세포들이 신경세포로 분화하는 것을 발견하였다. 특히 염색되지 않은 세포들이 증식하는 것도 관찰되었으며, 신경세포로 분화한 세포의 숫자에 비해 의미 있는 기능적인 회복이 일어난 것으로 보아 이식된 간엽줄기세포들은 전이분화(transdifferentiation)되어 신경계를 구성하는 세포를 재생하는 효과 이외에도 내인성 뇌 조직에 대해 자극을 하는 효과가 있으리라는 추측을 할 수 있게 되었다<sup>13</sup>.

임상적 치료에 이용될 수 있는 신경 세포의 획득을 위한 다양한 노력이 시도되고 있는 바, 제대혈 줄기세포에서 신경세포로의 분화 성공으로 획득에 용이한 이들 세포를 이용한 치료법 개발이 임상적 치료 관점에서 관심이 고조되고 있는 실정이다.

### 1) 뇌졸중(Stroke) 치료 연구

뇌졸중의 경우 통계청 자료상 우리나라 순환계 질환 질병 사망률 1위로 자리 잡은 무서운 질병으로 뇌졸중 후유장애로 고통 받는 환자가 점점 늘고 있어 개인적, 사회적, 국가적 차원의 막대한 인적, 물적 손실을 초래하고 있다. 이러한 질병 치료의 궁극적인 치료법은 손상된 신경 세포를 기능성 신경세포로 대체하는 것이며, 이에 대한 줄기세포 연구가 최근 활발히 진행되고 있고, 많은 환자들은 희망에 부풀어 있는 것이 사실이다. 그러므로 제대혈유래 간엽줄기세포와 골수간엽줄기세포를 이용한 치료법 개발이 절실히 요구되고 있으며, 이는 뇌손상으로 인한 장애 치료에 획기적인 전기를 이룩하게 될 것이다.

본 연구진은 허혈성 뇌졸중을 일으킨 흰쥐에 제대혈유래 간엽줄기세포를 이식한 후 행동학적 평가, 이식 세포의 생존과 병변부위로의 이동 및 분화를 통해 간엽줄기세포의 이식 효과를 알아보고자 하였다. 흰쥐의 뇌졸중 모델에서 허혈이 일어난 반대편에 이식된 줄기세포들이 이식 4주 후에 경색부위 주변에서 확인되었으며, Adhesive-removal test와 Rotarod test를 수행하였을 때 PBS를 투여한 대조군에 비해 간엽줄기세포를 이식한 실험군에서 행동학적 기능이 향상되었다. 그리고 병변부위 주변에서 발견된 세포 중 일부는 NeuN과



**Fig. 3.** Human umbilical cord blood-derived mesenchymal stem cell therapy for stroke in rat. (A) Behavior test (Adhesive-removal, Rotarod). (B) Migration of PKH26-labeled MSC toward infarct region *in vivo*. (C) Transdifferentiation of transplanted MSC in the brain of stroke model *in vivo* (NeuN, GFAP).

GFAP 표지인자에 양성을 나타냈다. 이를 통해 제대혈유래 간엽줄기세포가 허혈성 뇌졸중 동물모델의 기능 회복에 긍정적인 영향을 미치며 세포 치료제로서 사용될 수 있다고 사료된다<sup>14</sup>(Fig. 3).

또한 이러한 동물모델에서의 결과를 바탕으로 하여 본 연구진은 뇌졸중 환자를 대상으로 한 동종 제대혈유래 간엽줄기세포의 안정성 평가 및 효과 관찰을 위한 연구자 임상시험을 수행 중이다.

## 2) 척수손상 질환(Spinal cord injury) 치료 연구

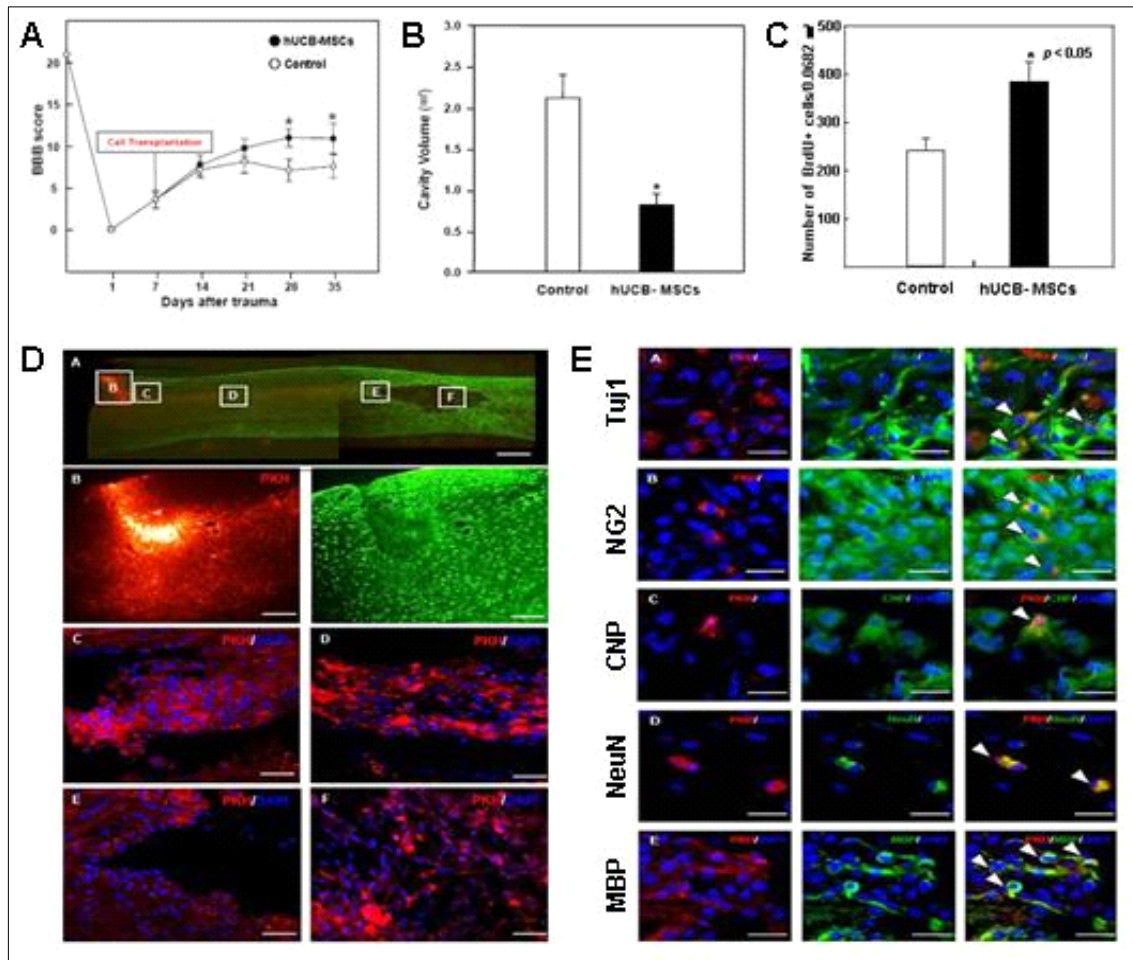
난치성 질환 중 척수손상 질환의 경우, 일차적으로 척수에 가해지는 물리적인 손상과 이차적으로 발생하는 일련의 감염과 excitotoxic damage를 통해 상처부위의 신경세포 뿐만 아니라, 이 보다 더욱 심각하게 descending 과 ascending axonal pathway를 파괴하여 영구적으로 감각, 운동 그리고 자율신경계의 기능을 상실케 한다.



## 특 강

척수손상 회복을 증진시키기 위해 크게 ① 신경세포의 생존, ② axon의 성장 또는 재생, ③ 자라는 axon의 정확한 방향성 인지, ④ 정확하고 기능적인 시냅스(synapse)의 재건이라는 네 가지 분야에서 다양한 노력이 진행되어 왔으며, 손상된 신경세포를 복구하고 단절된 axon 및 synapse를 재건하기 위한 가장 효율적인 방법으로 줄기세포를 이용한 세포치료법이 대두되고 있다.

본 연구진은 흰쥐의 척수손상 모델에 제대혈유래 간엽줄기세포의 이식에 따른 효과를 행동학적 움직임, 공동 용적(cavity volume), 그리고 손상 부위로의 간엽줄기세포의 이동 정도를 통해 알아보려고 하였다. 우선 줄기세포 이식부위에 있어서는 caudal이나 epicenter 부위에 이식한 군보다 rostral 부위에 이식한 군이 행동학적 움직임에 대한 test (BBB score)에서 기능 향상이 더 좋았으며, 공동용적이나 손상부위로의 이동에 있어서도 손상부위의 rostral에 이식치료를 수행하였을 때 더 효과가 있음을 확인하였다<sup>15</sup>. 또 다른 실험에서는 간엽줄기세포를 이식한 군에서 운동신경의 기능을 나타내는 BBB 점수가 향상되는 것을 확인하였는데, 이는 BrdU 양성인 세포들이 증가하는 것으로 보아 이식된 줄기세포에서 발현하는 여러 가지 성장인자들에 의한 간



**Fig. 4.** Human umbilical cord blood-derived mesenchymal stem cell therapy for spinal cord injury in rat. BBB score representing functional recovery (A), cavity volume (B), and counting of BrdU+ cells (C) after transplantation of MSC. (D) Migration of PKH26-labeled MSC toward injured region of spinal cord in rat. (E) Transdifferentiation of transplanted MSC in spinal cord injury model *in vivo* (Tuj1, NG2, CNP, NeuN, and MBP).

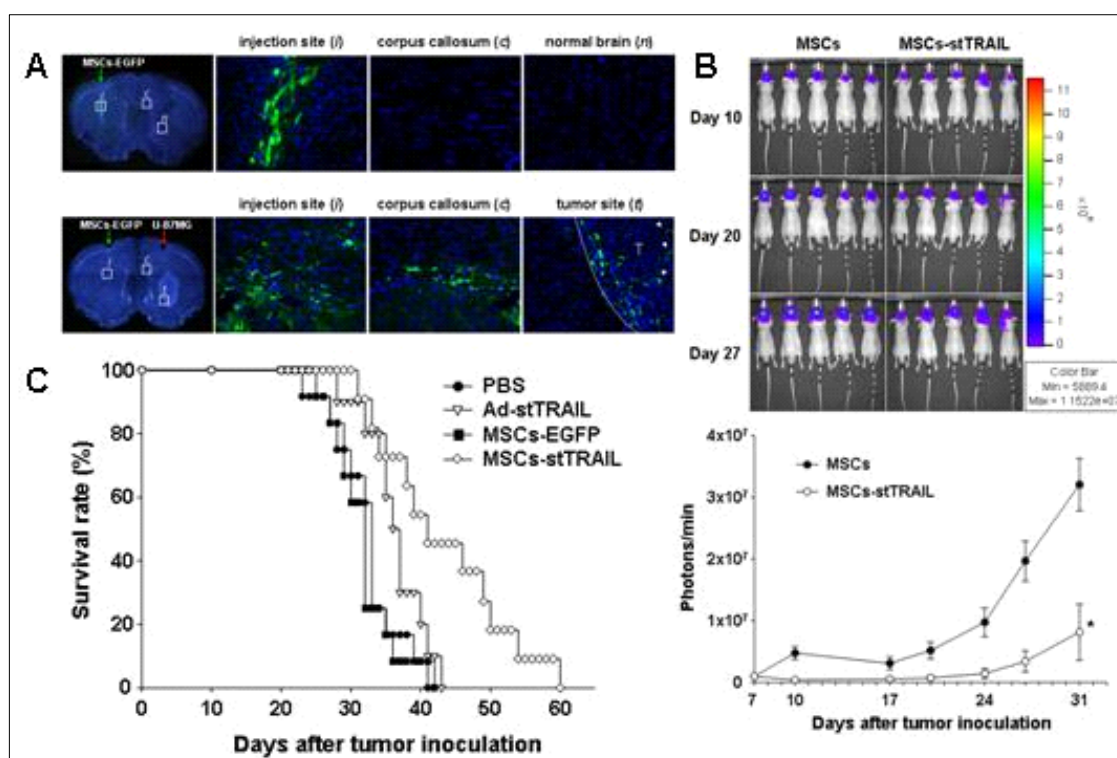
접적인 영향으로 내인성 신경세포의 증식을 촉진시키는 것으로 사료되며, 또한 이식된 줄기세포 자체도 신경 세포 관련 마커들에 양성반응을 나타내는 것으로 보아 신경세포로의 분화도 가능할 것으로 보인다(Fig. 4).

### 3) 뇌종양 (Glioma) 치료 연구

세포를 이용한 유전자 전달기술(cell-mediated gene therapy)은 바이러스 벡터 등에 의해 유전자가 전달된 세포를 국소 또는 전신 투여하는 세포 치료 기술이며, 최근 줄기세포를 이용한 유전자 치료가 많이 시도되고 있다. 특히 암에 있어 이러한 줄기세포를 이용한 치료는 암 병변을 찾아 가는 줄기세포의 능력, 즉 homing effect (attraction to cancer)를 이용하여 세포사멸을 유발하는 유전자나 면역체계를 활성화 시키는 사이토카인 (cytokine) 유전자를 운반하는 운반체 (gene vehicle) 역할로 사용되고 있다.

뇌종양에 대한 tropism은 신경줄기세포에서 우선적으로 증명되었으나, 최근 획득과 이용에 유용한 간엽 줄기세포 역시 신경줄기세포와 유사한 tropism을 보여주고 있어 신경줄기세포의 윤리적 및 획득의 제한점을 극복할 수 있는 훌륭한 대안으로 여겨지고 있고, 또한 유전자의 운반체로 종양까지 정확하고 안전하게 운반할 수 있는 능력이 있어 최근에는 사람의 간엽줄기세포를 이용한 유전자 치료 연구가 활발히 진행 중이다<sup>16</sup>.

본 연구진은 사람의 제대혈유래 간엽줄기세포에 강력한 항암효과를 보이는 변형된 TNF-related apoptosis inducing ligand (TRAIL) 유전자를 이입하여 뇌종양 동물모델에서 그 효과를 확인하였다. 우선 유전자가 이입



**Fig. 5.** Gene therapy using TRAIL-secreting human umbilical cord blood-derived mesenchymal stem cells against intracranial glioma. (A) Migration of UCB-MSCs towards gliomas *in vivo*. (B) Bioluminescent images revealing tumor growth of glioma-bearing mice treated with either MSCs-stTRAIL or MSCs and quantified bioluminescence intensities. (C) Survival curve of intracranial glioma-bearing mice.

## 특 강

된 간엽줄기세포를 뇌종양 동물모델의 종양형성부위 반대편 뇌에 이식하였을 때 이 세포들이 종양부위로 이동하는 것을 관찰하였고, 또한 TRAIL 유전자가 이입된 간엽줄기세포를 투여한 쥐의 생존률 및 종양 크기 분석 결과 대조군에 비해 뛰어난 항암 효과를 보이는 것을 알 수 있었다(Fig. 5). 따라서 간엽줄기세포를 이용한 유전자 전달 치료는 주변 정상 조직으로 침윤(infiltration)하는 종양세포를 따라 이동하여 죽일 수 있는 장점이 있어 바이러스를 직접 투여하는 유전자 치료보다 그 효과가 더 좋다고 할 수 있겠다(submitted data).

### III. 결론 및 전망

배아줄기세포는 사람으로 성장할 수 있는 배아를 파괴해야 얻을 수 있다는 점에서 생명윤리 논쟁이 빚어지고 있다. 이에 반해 성체줄기세포는 이러한 논쟁을 피해갈 수 있어 세포 치료의 최적의 대안으로 떠오르고 있다. 특히 제대혈 내 간엽줄기세포의 존재가 확인된 만큼 줄기세포 치료에 중요한 공급원이 된 것이 사실이다. 또한 제대혈의 특성과 이식의 임상적 문제점 및 보관 방법까지 모든 분야에서 연구와 개발이 빠르게 발전하고 있으므로 제대혈유래 간엽줄기세포 이식을 통한 환자의 치료에 기대를 걸고 있다.

줄기세포 치료에 있어서 환자에게 이상적인 치료를 위해서는 적절한 세포 및 이식방법 등에 대한 다양한 문제점들이 있다. 그리고 줄기세포 응용기술은 현재 세계 각국에서 급속히 발전하고 있는 분야이며, 지금보다 범위가 점점 확대되어 나가는 추세이다. 지금까지 많은 연구 결과, 장기 일부의 재생이나 기능의 회복에 효과가 있는 것으로 보고되고 있지만 결국에는 환자에게 적용되어 얼마나 충분한 치료의 효과를 거두느냐가 관건이다. 따라서 무엇보다도 줄기세포 자체에 대한 연구와 이해가 선행되어야 하며, 이를 바탕으로 기능적인 세포 치료제를 개발하는 것이 중요하다고 하겠다.

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## The Influence of Human Mesenchymal Stem Cell on Apoptotic Neuronal Cell Death

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**Objective:** To investigate influences of human mesenchymal stem cells (hMSCs) on apoptotic cell death in SHSY5Y cells (human neuronal cell line) in vitro.

**Materials and Methods:** Human bone marrow derived MSCs were prepared according to the institutional IRB-approved protocol and their characteristics for stem cells were confirmed with evaluation of surface markers using flow cytometry before experimental use. Apoptotic cell death was induced in SH-SY5Y cells following exposure to the non-specific protein kinase inhibitors staurosporine (STS, at concentrations of 0.25-2uM for 3-24hrs). After induction of cell death, hMSCs were co-cultured with transwell co-culture system for 5 days. Cell viability was assessed by Trypan blue dye exclusion method and MTS assay. Morphologic characteristics were observed with phase contrast microscope. Expression of cell survival related genes and caspase-3 activity were also evaluated.

**Result:** At concentration of 0.25 uM STS for 24hrs, cell viability of SH-SY5Y cells were 70-80%. After induction of cell death, we co-cultured SH-SY5Y cell lines with hMSC (transwell). When SH-SY5Y cells were co-cultured with hMSC for 5 days, the apoptotic cell death was delayed significantly than control ( $p < 0.05$ ). Morphological characteristics of apoptosis and caspase-3 activity were markedly decreased in SH-SY5Y cells were co-cultured with hMSC. Cell survival related gene expressions were changed.

**Conclusion:** We demonstrated that hMSC can increase cell survival and promote neurite outgrowth in the SH-SY5Y cell lines. These data may support the potential therapeutic application of hMSCs in neurologic disorders.

# Spontaneous Intracranial Hypotension: Clinical Presentation, Practical Features & Treatment

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**Objective:** Spontaneous intracranial hypotension (SIH) has become a well-recognized clinical entity, but sometimes it presented an uncommon clinical forms. The authors investigate clinical, MRI, and radioisotope findings and therapeutic outcome of the SIH

**Methods:** Restrospective review of 12 patients with the syndrome of CSF hypovolemia was done. Diagnostic tools were CSF tapping and measureing of opening pressure, radioisotope cisternography, Brain and Spinal MRI, CT myelogram.

**Results:** All patients had an headache with postural change, pachymeningeal enhancement on T1-weighted MRI image, 5 patients showed CSF leakage sites on radioisotope cisternography. In 7 cases, epidural blood patch was performed. If the epidural blood patch fails, blood patch was repeated to be symptom free.

**Conclusion:** First, it is important to have impression of SIH. Radioisotope cisternography and brain MRI c T1 enhancement are best diagnostic tools. Bed rest and autologous epidural blood patch are treatment of choice.

## Medical Thermography for Neurosurgeon: Present and Future (Focused on Functional & Stereotactic Neurosurgical Field)

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**Objective:** There has been more than 50 years since medical thermography was first introduced and during last several years there has been great advancement both in technical and software program. The object of this study is to review up-to-dated developments, scientific proofs, reasons for reconsidering its use, and future direction for neurosurgical field along with personal experience, especially focused on functional and stereotactic field.

**Materials and Methods:** Electronically searchable articles in literature were first acquired through Medline under headings of “thermography” or “thermogram”. All articles were categorized and indexed into various clinical fields and later subcategorized with respect to the field related to neurosurgery. Citations that contained controversial points on its usefulness versus drawbacks were collected in separate fields. Sensitivity, specificity, predictive values, and usefulness in various clinical settings, including neurological and neurosurgical disorders, were also evaluated. Current and future application projects that are under development by authors and others are than reviewed for the interest of neurosurgeons.

**Results:** A total of 5500 references were retrieved and reviewed from the literature that have been published up to year of 2007. The main reasons for sharp decline of its use until recent years were indiscreet use without standardized protocol, too much expectation but no regulation, poor sensor quality and poor imaging processing, poor understanding of physiological mechanism of thermal sensing technique and various clinical disorders, and lobbying effects of major insurance industry. However, with current modernized hardwares and softwares for the image acquisition, standardized protocol, and better understanding of physiologic mechanisms various disorders including neurological disorders and pain it seems reasonable to reconsider its use in many clinical settings, especially for the neurosurgeons. Some of in-progress projects that are under development by author and others are automated 3-D image reconstruction, image fusion, automated add-on diagnostic software using pattern recognition, pain pattern analysis with thermography, portable IR probe for microsurgical and microvascular surgery, and dynamic and functional imaging technique. These will aid in diagnosis of many disorders that were not completely understood from other diagnostic modalities. Also, they will help to monitor the therapeutic effects or the completeness of interventional and surgical treatments.

**Conclusions:** Despite many inherent limitations and disadvantages related to infrared thermography in medical field, author believes that it can be a very useful tool in selected neurosurgical fields when strict protocol of its usage is applied not only because it has several invaluable potential advantages but also its technology has been improving and many new ancillary appealing features.

# Behavioral and Histochemical Consequence of Selective Immunolesion in the Rats for Dementia Animal Model

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The cholinergic system has been widely implicated in cognitive processes and cholinergic loss is a classical hallmark in Alzheimer disease (AD). A monoclonal antibody to the low-affinity NGF receptor, 192-IgG, coupled to a cytotoxin, saporin, was recently introduced as an efficient selective neurotoxin for the NGFr-bearing cholinergic neurons in the rat basal fore brain. The present study, histochemical experiments were performed in slices from sham (Dulbecco's phosphate buffered saline) 192 IgG-saporin (SAP) treated rats to check the efficacy of the intracerebroventricular (ICV) injection of the immunotoxin. SAP lesion induced ICV injection lead to significant changes in cholinergic markers in the basal nucleus, medial septum, frontal cortex and hippocampus. The SAP treated rats were impaired in the acquisition of the water-maze task. Our data suggest that basal forebrain cholinergic hypofunction in ICV injection produces memory impairment in water maze task and this animal model may be useful to investigate some cognitive deficits in AD and further investigation is required of electrical stimulation to treat AD.

**Key words:** 192-IgG-Saporin, Cholinergic neuron, Morris water maze, Memory impairment, Electrical stimulation

# Clinical Application of the Brushite Calcium Phosphate Cement (Poly Bone) for the Surgically Induced Skull Bone Defects

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**Objective:** Skull bone defects were usually awesome to the patients and surgeons due to cosmetic problems especially. For a long time, polymethylmethacrylate bone cement (PMMA) was used as a bone filler especially in the calvarial region. But high polymerization temperatures (900C), toxic liquid, low biocompatibility and lack of bone bonding effect of PMMA bone cement make them a material of second choice.

In the recent years, the use of calcium phosphate cements is becoming more common in craniofacial surgery because of the high biocompatibility, osteoconductive activity, no exothermic reaction and no need of fixation device such as wire or plate due to bone bonding effect..

New developed calcium phosphate cements (PolyBone, kyeung-won med. Seoul, Korea) was used as a bone mineral substitute to repair the surgically induced bone defects in cranium.

**Materials and methods:** The cement was used for postoperative bone defects occipital regions in cases of MVD (5 patient).

**Results:** There was no inflammatory reaction surrounding the implanted materials and no air or CSF leakage. The defect fillings and augmentations were successful in all patients. From the check-up radiographs, the material could be seen as a dense, radio-opaque structure without the material artifacts.

**Conclusion:** We have demonstrated that new developed brushite calcium phosphate cement is biocompatible, alloplastic material that is useful to repair and augment the surgically induced bone defects for cranio-facial surgery especially for moderate-size defects of the calvaria and facial bone

## SCENAR Therapy for Fibromyalgia

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Fibromyalgia is a chronic musculoskeletal syndrome characterized by diffuse pain in absence of synovitis or myositis. Associated symptoms include fatigue, sleep disturbances, headaches, irritable bowel syndrome, paresthesias, cognitive disturbances, depression and anxiety. The incidence of this syndrome is high, however this syndrome is not well-controlled by medication, physical therapy and other pain management programs. The authors performed SCENAR(Self Controlled Energo Neruro Adaptive Regulator) therapy for fibromyalgia.

Twenty one (M:F=2:19) fibromyalgia patients were treated by SCENAR from September 2007 to February, 2008. They were diagnosed by criteria for the classification of fibromyalgia (ACR, 1990).

We performed general technique with local application SCENAR methods for these patients. The mean number of treatment was 8.5 (4-15) and mean treatment time was 42 minutes. We defined result of treatment as excellent (VAS post-Tx/VAS pre-Tx  $<0.2$ ), good (VAS post-Tx/VAS pre-Tx  $<0.5$ ), fair (VAS post-Tx/VAS pre-Tx  $<0.7$ ), and poor (VAS post-Tx/VAS pre-Tx  $\geq 0.7$ ). The treatment results were as follows excellent 41%, good 17%, fair 25% and poor 17%.

SCENAR therapy, especially general technique is one of a good treatment tool for pain control in fibromyalgia.

## Our Experience of Spinal Cord Stimulation for Intractable Spinal Pain Patients

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**Objective:** Spinal cord stimulation (SCS) has been documented as effective treatment for those with chronic back pain, diabetic neuropathic pain, CRPS, and failed back surgery syndrome (FBSS). However, the effectiveness of SCS for pain from spinal cord injury (SCI), is debatable. We describe our experience of SCS in a patient suffering from intractable spinal pain.

**Material and Method:** Between January 2001 and december 2007, 6 patients (Mean age: 64, M:F 2:4) with 4 SCI patients, 1 FBSS, and 1 transverse myelitis underwent surgery. First surgery was performed to insert electrode and test therapeutic effect by laminectomy and insertion of surgical type electrode to the thoracic epidural space. When the pain relief was confirmed during 2 or 3 days of stimulation trial, the second operation for battery insertion was performed.

**Results:** Two patients with SCI and 1 patient with FBSS were not effective for pain control and electrodes were removed after test stimulation. Three other patients (2 SCI and 1 transverse myelitis) underwent battery insertion and the pain was improved.

**Conclusion:** Chronic pain is a complex condition that requires a multi-disciplinary approach to management. SCS has evolved into easy reversible technique with low morbidity for the management of chronic pain. Although, SCS is not generally helpful with pain from SCI, as with our experience, it could make therapeutic effect in some cases. We suggest that SCS can be recommended for pain from SCI when all other treatments are failed.

**Key words;** Spinal cord stimulation, Chronic pain, Spinal cord injury



## 중추성 및 말초성 신경병성통증에 대한 운동피질자극술

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**Objective:** Neuropathic pain is the pain syndrome caused by injury or dysfunction in the nervous system, i.e. central and peripheral nervous system. Although medical treatment is quite effective for neuropathic pain, there was still some patients suffering intractable chronic neuropathic pain. Motor cortex stimulation (MCS) was first proposed for the treatment of central poststroke pain, and has been shown to be effective in relieving peripheral neuropathic pain (e.g. trigeminal neuropathic pain, brachial plexus avulsion, phantom pain). Although modulation of thalamic activity is regarded as a possible pathophysiologic mechanism of MCS, the application of MCS is mainly empirical and still limited. The authors report our experience of motor cortex stimulation (MCS) in patients with medically intolerable central and peripheral neuropathic pain.

**Material and Method:** During the last 4 years, 10 patients underwent MCS trial for intractable central and peripheral neuropathic pain. The cause of central pain was traumatic brain contusion (2), spinal cord injury (2 cervical, 1 thoracolumbar), iatrogenic surgical cervical cord injury (postcordotomy dysesthesia), brachial plexus injury, complex regional pain syndrome type II, poststroke pain (3). Their pain did not respond to maximal medical treatment including anticonvulsant, antidepressant, and opioid. The duration of pain ranged from 2 to 35 years. Under the 3D neuronavigational guidance, about 5 centimeter-sized craniotomy was done parallel to the central sulcus and the sagittal sinus. Epidural SEP monitoring and direct cortical stimulation were done to localize the exact somatotopy of motor homunculus. For the arm and trunk pain, laminotomy electrode was placed parallel or perpendicular to the precentral gyrus, and for the leg pain another electrode was placed parallel to the sagittal sinus. Trial stimulation was given with varying stimulating parameters for 3-7 days. If the patient's pain relief was more than 50%, the implantable pulse generator was implanted.

**Result:** For hemibody pain following TBI, MCS showed excellent pain relief with more than 3 years follow-up. For arm pain with iatrogenic cervical cord injury, postcordotomy dysesthesia and brachial plexus injury pain MCS was effective with 50% pain relief with more than 1 year follow-up. In patients with leg pain following spinal cord injury, MCS was effective in one of three patients. MCS was effective in one of poststroke pain with more than 2 years follow-up. In one TBI central pain patient, we could discontinue all analgesic medication. However, in remaining other patients with even successful MCS implantation, the patients still need large amount of anti-convulsant and opioids. In our trial MCS, trial success was about 60% (6/10) and in the early responders, 2 patients showed varying degree of tolerance, and one needed revision (subdural placement of epidural electrode). There was no complication related to the procedure or stimulation itself (mean follow-up 18 months).

## 일반연제

**Conclusions:** As shown in these patients, MCS was effective in some patients with intractable central and peripheral neuropathic pain. We felt that MCS was more effective for peripheral neuropathic pain than the central pain syndromes and arm pain responded better than leg pain. Concerning that spinal cord injury pain is one of the most difficult pain to treat, we think we should seek another effective means to control. Further application of MCS and sophisticated treatment is warranted for this chronic intractable pain syndrome.

## Double Specify SCS for CRPS, type 2

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**Objective:** CRPS management includes specific detail with concurrent, interdependent, and sequential increments. We assessed with totally resistant CRPS type 2 who remain in severe pain and disability despite all other therapies. Among one of them, operated cervical and low thoracic specify SCS, 1.5 year interval.

**Material:** A 42-year-male patient had spinal cord injury after fall down. All extremities pain (esp. Both legs pain) was severe and CRPS symptom was developed, 10 years later.

**Result:** All treatment was not effective for him, he received low thoracic spinal cord stimulation operation in Jan-2006. His symptom was improved from VAS 10 to VAS 3. But, both wrists and hands pain was aggravated and then. So, he received many therapies, but it was not effective. He received low cervical spinal cord stimulation in July-07. His VAS was improved from 10 to 5.

**Conclusion:** Spinal cord stimulation is very effective for intractable CRPS patients.

**Key words:** CRPS, Spinal cord stimulation, Pain

## Patient Self-Reported Outcome in Cubital Tunnel Syndrome

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**Objective:** Cubital tunnel syndrome (CuTS) is the second most common entrapment neuropathy after carpal tunnel syndrome. Previous studies have used quantitative physical assessments to report outcome after surgery. However, patient subjective report is also important to assess the outcome. This study assessed subjective outcome in patients with cubital tunnel syndrome who were underwent surgical intervention.

**Method:** 31 patients who underwent surgical intervention for CuTS between 2000 and 2007. The patients included 7 females and 24 males, and the average age was 47.3 (range, 32-67) years. The affected side was the right elbow in 13 patients, the left elbow in 15 and the 3 patients were bilateral. Average follow-up period was 14.6 (range, 10-27) months. According to Dellon's classification, 23 patients were severe, 7 patients were moderate and 1 patient was mild grade. Grip strength was tested by using the Jamar Dynamometer (Smith and Nephew, Memphis, TN). Post-operative outcome assessment was based on the modified Bishop rating system. Subjective outcome was assessed using a questionnaire.

**Results:** Postoperatively symptoms were significantly less than those preoperatively: pain,  $p=0.001$ ; tingling,  $p=0.085$ ; and numbness  $p=0.013$ . In 19 cases, patients reported normal sensation and in 10 cases, patients reported normal strength. The authors found no differences in grip strength in 20 cases. Four patients showed fair results based on modified Bishop rating system. 27 patients were satisfied with the post-operative results.

**Conclusion:** Results following surgical management of cubital tunnel syndrome vary by report and other factors such as surgical technique, age, compensation and litigation. Although objective outcome measures such as grip strength showed no improvement, subjective functional recovery can be achieved.

**Key words:** Cubital tunnel syndrome, Outcome assessment

# Brachial Plexus Injury에 대한 DREZ Operation 직후 발생한 Whole Body Complex Reflex Pain Syndrome - 증례 보고 -

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44세 남자 환자로 내원 5년 전에 교통사고 후에 좌측 상지의 brachial plexus injury 및 상지 마비가 발생된 후, 시간이 경과하면서 deafferentation pain이 발생됨. 이에 대한 약물 치료, 신경차단치료, spinal cord stimulation 등의 치료를 시도하였으나, 효과가 없었다.

환자는 전신 마취 하에 DREZ operation (C3-T1, Sindau method)을 시행하였다. 마취에서 회복되면서, 심한 전신의 전신 통증(지속적이고 발작적인 칼로 찌르는 듯, 쪼이는 듯한 양상)을 호소하였다. 다한 증상을 동반하였으며, 수술 부위 통증은 호소하지 않았다. 수술 후 운동 신경 기능은 정상이었다. 마약성 진통제를 포함한 진통제, 항전간제, 항우울제 등의 약물은 고용량의 투여에도 증상은 반응을 보이지 않았다. Barbiturate coma therapy (2 weeks)를 시도 하였다. 환자는 Barbiturate coma therapy에서 깨어나면서 불인성 통증과 관련한 증상이 안정되었고, 환자는 걸어서 퇴원하였다.

본 환자에서의 임상 경험을 보고하고 토론하고자 한다.

## Technical Considerations about MicroDREZotomy for Paraplegic Pain

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It is well known that control of pain due to spinal cord injury is difficult but the microDREZotomy (MDT) is the best choice of treatment modality.

With regard to the technical principles by Sindou, MDT consists of an incision followed by bipolar coagulations performed ventrally at the entrance of the dorsal rootlets into dorso-lateral sulcus of the cord. The number of operated cord segments is variable but generally depends on the pain dermatomes. He reported that diffusely infrasegmental pain was not controlled with MDT. Other authors presented that the characteristic pain nature for good outcome were segmental, mechanical and/or intermittent pattern. Several reports presented that overall good outcome of MDT for paraplegic pain was over 50%.

Today author would introduce the technical experiences for improvement of surgical outcome of control of paraplegic pain.

Blunt insult to spinal cord resulted in various features of scar formation with or without cystic lesions. If patient complained segmental pain, MDT was done on the cord level according to pain distribution as like traditional technique. But if patient suffered from infrasegmental, thermal and/or continuous pain, I performed the traditional procedure and also focused on the injured and scarred cord level. I tried to cut every injured and fused rootlets and MDT was performed along the imaginary postero-lateral sulcus on injured spinal cord. If the patient was on complete paraplegic state, I cut the both dorsal column also. These procedures would be very helpful to control the paraplegic pain of the patient who suffered from the infrasegmental, thermal and/or continuous pain.

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# Percutaneous Balloon Compression of Trigeminal Ganglion for the Treatment of Idiopathic Trigeminal Neuralgia: Experience in 50 Patients

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**Objective:** We assessed the surgical results of percutaneous balloon compression in 50 patients with idiopathic trigeminal neuralgia and classic pain.

**Methods:** Fifty patients with follow-up of more than 12 months were retrospectively analyzed. The mean follow-up period was 42 months (range, 12-82). The mean age was 65.8 years (range, 27-83). Seventeen patients (34%) had other previous surgical procedures. The balloon was inflated by injecting radio-contrast media under brief general anesthesia according to Mullan's technique. The mean inflating time was 88 seconds (range, 60-120). The whole procedure took about 20 minutes

**Results:** We reported excellent and good results in 70% of the cases, poor in 6% as annoying dysesthesia, recurrence 16%, and 8% had initial failure due to technical deficiencies. Forty-six patients (92%) were initially relieved of their pain. There were permanent motor weakness of the masseter muscle in 4% of patients and transitory diplopia in 8%. Neither anesthesia dolorosa nor keratitis occurred. Almost all patients (92%) were discharged postoperatively within two days.

**Conclusion:** This study shows the procedure would be an effective method with acceptable morbidity, technically, it can be performed rapidly and simply in the treatment of idiopathic trigeminal neuralgia.

## Surgical Treatment of Entrapment Neuropathy of Lateral Femoral Cutaneous Nerve (LFCN); Meralgia Paresthetica (MP)

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Entrapment of the lateral femoral cutaneous nerve (LFCN) as a source of anterolateral thigh dysesthesia has been recognized for more than 100 years. Despite this historic recognition, its diagnosis today is often delayed, and definite treatment of refractory cases by surgical decompression rarely reported. This study describes 10 LFCN entrapments in 9 patients whose etiologies include idiopathic cause, iliac bone graft harvesting, seat-belt injury associated with motor vehicle accident, and diabetes.

A retrospective analysis of 9 patients with intractable meralgia paresthetica (MP) was completed. 5 women and 4 men were included. The mean age of patients at time of surgery was 37 years. Duration of symptoms prior to surgery ranged from 6 months to 3 years. Postoperative follow-up has been obtained up to 33 months, with a mean of 9 months. MP patients whose pain relieved with medical treatment was excluded.

The diagnosis of MP is based on sensory symptoms occurring in the distribution of the LFCN and nerve conduction studies of the LFCN, and repeated blocks of LFCN. For the surgical decompression, about 5 centimeter-sized incision was made over the course of LFCN and point of maximal tenderness. The nerve was usually 1 centimeter medial to the anterior superior iliac spine. LFCN was released with excision of all overlying and underlying fascias. The inguinal ligament was not reconstructed.

Results were judged as follows; excellent, complete relief of symptoms and return to work; good, partial relief of symptoms; and poor, no relief of symptoms. Of the 9 patients, excellent results were obtained in 8, good in 1. There was no complication.

Diagnosis of meralgia paresthetica is sometimes difficult and confusing. Careful history taking and diagnostic blocks are essential in the diagnosis of MP. If the diagnosis is correct, surgical decompression of LFCN could be an excellent treatment for chronic, disabling entrapment.



## Trigeminal Neuralgia Associated with the Clival Osteochondral Dysplasia; Anomaly of the Craniovertebral Junction

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**Objective:** The cause of idiopathic trigeminal neuralgia (ITN) has not been fully explained. Vascular compression of the trigeminal nerve in the cerebellopontine angle is now generally accepted as the primary source causing TN. However, the reported percentages of cases without neurovascular conflict vary from 1.4% to 28.5%. In a small number of cases, TN has been reported to be associated with deformity at the skull base. All the reported cases of TN associated skull base deformity are caused by basilar invagination, i.e. prolapse of vertebral column into the posterior fossa. We report a TN caused by clival osteochondral dysplasia and tortuous basilar artery, a case of TN with craniovertebral junction anomaly without basilar invagination.

**Methods:** A 36 year-old male presented a severe chronic TN in his left V2,V3 dermatome of 2 years duration. His pain was very intense and his VAS was about 6-7/10. He had a tic attack everytime in speaking, chewing, and tooth-brushing. At the time of referral, his medication was gabapentin 2,700 mg, carbamazepine 1,200 mg, oxycontin 40 mg, tramadol 150 mg, acetaminophen 1800 mg, amitriptyline 30 mg. A plain skull x-rays, MRI scan and three-dimensional CT scan was done and we evaluated the cause of TN.

**Result:** An anomaly of the craniovertebral junction was detected. His head was dolichocephalic. The foramen ovale was seen intact. However, the clivus was severely dysplastic and small. The temporal petrous bone was elevated bilaterally. The right C1 lateral mass was hypertrophied and left of that was hypoplastic. The left vertebral foramen was not seen. However, platybasia or basilar invagination was not observed and Welcher's basal angle was about 131° degree, which was not exceeding the criteria of platybasia (143°). Basilar invagination was not seen even with the estimation with the Chamberlain line and McGregor's line. The right vertebral artery and basilar artery was very tortuous, and the left trigeminal root was distorted by ectatic basilar artery.

A percutaneous radiofrequency rhizotomy (PRR) was done under the fluoroscopic guidance. his TN relieved immediately but recurred at 3 months after PRR. A repeated PRR was performed with the same manner. However, pain relief was about 50% and he still need the same dose of preoperative medications until 1 year after repeated PRR.

**Conclusion:** This type of osteochondral dysplasia is very unique because it involved the clivus and petrosal bone, C1 and C2 with resultant crowding the posterior fossa without causing basilar invagination. A severely ectatic basilar artery was seem to be related to the etiology of TN with the craniovertebral junction abnormality. We think this case is very rare because it is not associated with basilar invagination. Further investigation is needed for the etiology of TN.

## Familial Leukodystrophy Caused Abnormal Movement Disorder and Pallidal Deep Brain Stimulation?

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**Objectives:** Leukodystrophy is a progressive disease of myelin which produces progressive motor abnormalities and mental deterioration, and results in severe disability. Most leukodystrophies are onset in early childhood. The leukodystrophies with adult-onset are rare. The authors report a rare case of familial adult-onset leukodystrophy. Intra-operative MER were used as support in selecting the target and the result of microelectrode recording(MER) during pallidal deep brain stimulation(DBS) surgery are discussed.

**Materials and Methods:** A 36-year-old man developed involuntary hyperkinetic movement of upper extremities about 9 years ago. His abnormal movement had deteriorated as a result of continuous choreoballistic movement and dystonia affecting whole extremities, trunk and neck. He was also developing mental deterioration with confusion and aggressive behavior of violence and restlessness over the course of 3 months. The symptoms eventually threatened his life. A brain MRI revealed diffuse symmetrical high signal intensities in periventricular subcortical white matter on T2 weighted image that strongly suggested leukodystrophy. His older brother 43-year-old man also transferred 1 year later because of abnormal motor symptoms and psychiatric symptoms for severe years. Comparison of his clinical and radiological findings with those from his brother showed good agreement. Bilateral pallidal DBS with microrecording in two brothers were performed under general anesthesia with propofol. Bilateral posteromedian hypothalamotomies were done simultaneously for the control of aggressive behavior of violence in young brother. Their parents, sisters and children did normal life without an abnormal movement disorder or a psychiatric symptom. Gene study showed negative for dystonia (DTY1) and metachromatic leukodystrophy.

**Results:** Globus pallidus internus (Gpi) signals in two brothers was obtained for selecting the target. Post-operative MRI confirmed electrode positions within the GPi. Good control was achieved for dystonia-dyskinetic syndrome. Neither major complications nor neurological deterioration.

**Conclusion:** The result in this cases demonstrate that pallidal DBS can dramatically improve abnormal hyperkinetic movement in leukodystrophy. Microelectrode recording in the globus pallidus internus in patients with leukodystrophy may be used as a valuable method in selecting the target.

## Hypothalamic Stimulation for Intractable Chronic Cluster Headache

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**Objective:** Cluster headache is a stereotypical primary pain syndrome characterized by strictly unilateral severe headache accompanied by ipsilateral autonomic phenomena. Recent studies revealed activation in the hypothalamus and therefore it became a target for therapeutic deep brain stimulation (DBS). The authors report a case of intractable chronic cluster headache in a 60-year-old man treated with hypothalamic DBS.

**Case Report:** He had been suffering from intractable cluster headache (VAS:9) for at least 2 year without remission, despite medical treatment, the classic surgical procedures such as open microvascular decompression (Feb. 28, 2006) and percutaneous balloon compression of trigeminal ganglion (Mar. 29, 2006). Using a stereotactic approach with MRI-guided and microelectrode recording, a quadripolar lead (DBS-3389; Medtronic) was inserted in the ipsilateral left posterior hypothalamus (Aug. 28, 2006). During the trial test a marked reduction in the severe orbital pain (VAS:2). After 5 days the stimulation device was implanted subcutaneously (Sep. 1, 2006).

**Result:** The postoperative follow-up was 24 months. The last following parameters were used for the cyclic stimulations: bipolar 0-1+; amplitude 1.5V; frequency, 185 Hz; pulse width, 60 milliseconds; cyclic mode, 1 hr "on" and 6 hr "off". VAS was on the average approximately 4.

**Conclusion:** Cluster headache patient can respond favorably to hypothalamic stimulation.

## Percutaneous Radiofrequency Trigeminal Rhizotomy after Recurrent Trigeminal Neuralgia Following Gamma-knife Radiosurgery

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**Objective:** Trigeminal neuralgia (TN) is a unique pain syndrome characterized by paroxysmal, lancinating pain over the dermatome of the trigeminal nerve. There are many surgical and percutaneous techniques for medically-refractory TN and each of them has advantages and disadvantages. Currently, gamma-knife surgery (GKS) is gaining a popularity with widespread use of equipment, and minimally-invasive nature of procedure. However, GKS has an disadvantage of recurrence like other percutaneous procedures. In case of recurrence after GKS, some authors recommended repeated GKS. However, due to risk of radiation injury, there are some debates in this matter. The authors report an effectiveness of percutaneous radiofrequency rhizotomy (PRR) in a case with recurrent TN after initially successful GKS treatment and discuss the technique.

**Methods:** A 71 year-old male patient presented a typical TN in V3 dermatome. He underwent GKS 1 year prior to PRR. His pain was typical TN and responded to GKS after 2 months after GKS, and about 50 % pain relief was obtained for about 6 months. However, his pain recurred to previous level after 1 year, and did not responded to carbamazepine and gabapentin. on examination and history, his pain did not seem to be related to that of radiation injury, but that of typical recurrent TN. A percutaneous radiofrequency thermal rhizotomy was performed under the fluoroscopic guidance. after verifying the lead location under fluoroscopic view, thermal lesion was made for 60 seconds in each 70°C, 75°C, 80°C.

**Results:** The operation took 30 minutes. There was no operative morbidity and the patient discharged with immediate pain relief at postoperative 6 hours. A moderate paresthesia with hypesthesia existed for postoperative 1 month and disappeared soon. The medication stopped at postoperative 1 month follow-up and he is pain-free with 2 year follow-up.

**Conclusion:** As shown in this particular case, percutaneous radiofrequency rhizotomy is quite simple and technically easy to control the lesion with experienced hands. We think that in case of recurrence after GKS, PRR can be an effective means to control recurrent TN.

## Deep Brain Stimulation for Treatment of Cervical Dystonia Concomitant with Head Tremor - A Case Report -

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**Objective:** Dystonia is a clinical syndrome characterized by sustained muscle contractions, frequently causing twisting and repetitive movements or abnormal postures. And Deep brain stimulation of the globus pallidus interna (GPi) has gained widespread acceptance over the last several years as an effective treatment for dystonia. Also, deep brain stimulation (DBS) of the VIM nucleus of the thalamus has been reported to be efficacious for reducing essential tremor. But it is difficult to determine the target for treating dystonia and tremor simultaneously.

**Case:** A 70-year old woman was admitted, complaining of left-side tilted neck and head tremor for several years. She had been treated with hypertension for 2 years. We performed right GPi lesioning and VIM DBS and left GPi DBS for treatment of dystonia and head tremor.

**Result and Conclusion:** After turning pulse generator on, her dystonia and tremor were almost disappeared. We report a good result for treatment of cervical dystonia concomitant with tremor using new technique.

## Suicide after Successful DBS for Parkinsonism

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**Objective:** Deep brain stimulation has been approved by the FDA for use in the treatment of Parkinson's disease, essential tremor, and dystonia. Whereas motor improvement has been consistently documented, cognitive dysfunction, mood changes, behavioral disturbances, and apathy have been occasionally reported.

**Material:** We operated 57 deep brain stimulation operations during last 5 years.

In the setting of a large deep brain stimulation program for parkinson's disease, all patients experienced an excellent motor outcome following the operation.

**Result:** A 43-year-old male patient suicided after successful both STN-DBS surgery. Another 69-year-male patient had received STN-DBS surgery in the another hospital.

His motor symptom was improved after DBS operation, but he suicided after operation.

**Conclusion:** DBS is an effective treatment for Parkinson's disease, but there is high rate of suicide in patients treated with DBS. Additionally, patients should be monitored closely for suicidal behavior postoperatively.

## Medial Thalamotomy for Poststroke Pain

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**Objective:** Medial thalamotomy has been used for treatment of somatic, deafferentation, and central pain. The rationale of using medial thalamotomy for neuropathic pain rests on the termination of the spinothalamic tracts in the medial thalamus.

**Materials and methods:** We assessed the effect of the medial thalamotomy for the poststroke pain. We operated medial thalamotomy for two poststroke pain patients. Male to female ratio was 1:1.

**Results:** All patients were all postinfarction pain. Preoperative VAS was 8.5, postoperative VAS was 4.

There was no complication.

**Conclusion:** Motor cortex stimulation is very effective for poststroke pain, but it is not covered by medical insurance. Medial thalamotomy is effective for poststroke pain.

**Key words:** Medial thalamotomy, Poststroke pain

## Neuromodulation for Intractable Visceral Pain due to Chronic Pancreatitis - A Case Report -

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Pain caused by chronic pancreatitis is frequently medically intractable and generally resistant to celiac plexus block. There have been recent studies in the literature that spinal cord stimulation(SCS) reduces pain of visceral nociception. We controlled pain by SCS in one case. We present here a case report and a review of the literature.

A 51-year-old man presented abdominal pain with diffuse upper thoracic pain for 3years. The patient had a history of multiple emergency room visits and repeated hospitalization. Pain control could not be achieved by nerve block. So we performed percutaneous lead implantation at T7-8 level. After 8 days stimulation trial, we performed laminectomy and electrode implantation. Patients experienced a decreased VAS scores for pain intensity and amount of opioid intake.

We suggest that SCS is a useful treatment option for abdominal visceral pain. And further studies and long term follow-up is needed.



## 수근관 증후군 정도 평가를 위한 자기 기입식 설문서

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Although carpal tunnel syndrome (CTS) is the most common entrapment neuropathy, there are few reliable and valid tools for assessment of clinical severity and outcome after treatment. A simple, uniform and easily administrable assessment tool is required for CTS. Several self-administered questionnaires have been developed, one of which is the Boston Questionnaire (BQ). This prospective study evaluates a Korean version of a self-administered questionnaire for CTS regarding reliability and validity.

Boston Questionnaire (BQ) was translated in Korean and slightly modified in order to achieve cross-cultural equivalence to the original version. The questionnaire was administered to patients who underwent surgery for CTS and examined for reliability including reproducibility (test-retest reliability) and internal consistency. Validity was evaluated using the Short Form-36 general health questionnaire (SF-36) and electrophysiologic studies.

The questionnaire was highly reproducible (Pearson correlation coefficient,  $r=0.82$  and  $0.78$  for severity of symptoms and functional status, respectively) and internally consistent (Cronbach alpha,  $0.80$  and  $0.83$  for severity of symptoms and functional status, respectively). BQ symptom severity and functional status scales correlated with SF-36 scales.

Modified Boston Questionnaire (MBQ) is a reliable and valid instrument for measuring the symptom severity and functional status in the patients with carpal tunnel syndrome.

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