J.W. Chang, Y. Katayama,
and T. Yamamoto (eds.)

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Advances in Functional and Reparative Neurosurgery

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Preface

This supplement of Acta Neurochirurgica is the fourth in the series of proceedings covering the official biennial conferences of the Neurorehabilitation Committee of the World Federation of Neurosurgical Societies (WFNS) in connection with the 1st congress of the International Society of Reconstructive Neurosurgery (ISRN) which was held in Seoul in September 1–3, 2005. This supplement deals with various forms of neuromodulation and neurorehabilitation therapies in the field of stereotactic and functional neurosurgery. Recent advances in stereotactic and functional neurosurgery have opened up an important new area in which neurosurgeons can collaborate with basic neuroscientists, engineers, and other specialists from diverse fields such as rehabilitation, ENT, eye, orthopaedic surgery etc. I have no doubt that the authors assembled to address these topics have presented a balanced and up-to date analysis of the knowledge and approaches in this new era. Furthermore, I am confident that this supplement has been conceived to provide timely and pertinent reviews of clinically and neuroscientifically relevant topics for the practicing neurosurgeons in this field.

I would also like to express my sincere and cordial thanks to Professor Katayama and Professor Yamamoto for their heartfelt cooperation and guidance in the accomplishment of this supplement and for the successful meeting. I would also like to thank all the authors for submitting their original papers for inclusion into this 4th supplement. Finally, I wish to say a special word of thanks to Professor Steiger, the editor of Acta Neurochirurgica, for his support and aid in achieving this supplement.

Jin Woo Chang
Congress President
4th Scientific Meeting of the WFNS
Neurorehabilitation Committees
1st Congress of ISRN

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Early rehabilitation of higher cortical brain functioning in neurosurgery, humanizing the restoration of human skills after acute brain lesions

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Summary

Objective. Increasingly more patients after brain damage survive, however, suffering from severe impairments of higher cerebral functioning.

Methods. Patients after acute brain damage, mainly secondary to TBI, are referred for early neurosurgical rehabilitation. Our concept follows the German Guidelines. It is based on a multidisciplinary team approach. Next-of kin are included in the treatment and caring.

Results. The essential aspect of early neurosurgical rehabilitation is the integration of disciplines and consistent goal setting to regard individual patients' needs. Good structural organization of the team, notice of basic communication rules, conflict management and a definite decision making increase productive interdisciplinary working. The film (shown at the symposium) shows how to humanize human skills after brain damage.

Discussion. Obviously the impairment of mental-cognitive and neurobehavioral functioning and not the loss of physical skills cause the patients' loss of life transactions and final outcome after brain damage. Our concept supports and fosters the individuals' neural plasticity and final social reintegration.

Conclusion. Functional rehabilitation is a process whereby patients regain their former abilities or, if full recovery is not possible, achieve their optimum physical, mental, social and vocational capacity. Neurosurgeons will have to work in close collaboration with the neuropsychologist and all other members of the interdisciplinary team day by day.

Keywords: Concept of early rehabilitation in neurosurgery; traumatic and nontraumatic brain damage; restoration of neurological and mental-cognitive, neurobehavioral functioning; team work.

Introduction

"Brain damage has become synonymous with loss of skills, while rehabilitation of brain damaged individuals has become known as method to restructure lives within a social context" as Anne-Lise Christensen (3 p XV) quotes.

Severe acute brain damage is a major ethical and social burden in the industrialized and in the emerging countries with regard to life-long disability, unnatural death, and the enormous social-economic costs. Most patients suffer from cranio cerebral injury (CCI) (mainly after accident and violence) and nontraumatic brain lesions secondary to stroke, intracranial subarachnoid and/or intracerebral hemorrhages, and tumours and increasingly secondary to cerebral hypoxemia and toxic insults [1, 2, 5–7, 9, 10, 15, 22, 25, 29, 30]. A head injury is often complicated by primary extracranial multiple organ lesions and early secondary complications requiring an interdisciplinary neurosurgical acute management and early rehabilitation. Advanced life support, intensive care treatment and emergency cranial computerized tomography (CCT) has enabled increasingly more patients to survive, in many cases, however, suffering from severe impairments of higher cerebral function [5, 10, 11, 14–16, 18, 23, 25, 28–30]. Mental neurobehavioral disability calls for a different degree of adjustment than does the need to cope with most physical disabilities [2, 3, 7, 9, 12, 15, 18, 25, 29]. This is why nowadays neurosurgeons have become more and more responsible to start off patient's holistic rehabilitation [2, 18], as it can be seen in the spectrum of neurorehabilitation (Fig. 1) [16, 29]. The author's concept with a specially designed department (Fig. 2) that is based on The German Task Force for Early Neurological Neurosurgical Rehabilitation (ENNR) and its Guidelines has been accepted and meanwhile followed in central Europe [16, 28]. ENNR is addressed: 1) to refer the patient as early as possible from the intensive-care unit (ICU) for ENNR in the same building and 2) to start the individually designed rehabilitative intervention very early on, 3) to promote functional recovery, brain plasticity, and compensation strategies [21], and 4) to prevent and treat frequent secondary and tertiary complications that keep the patient on the ward.

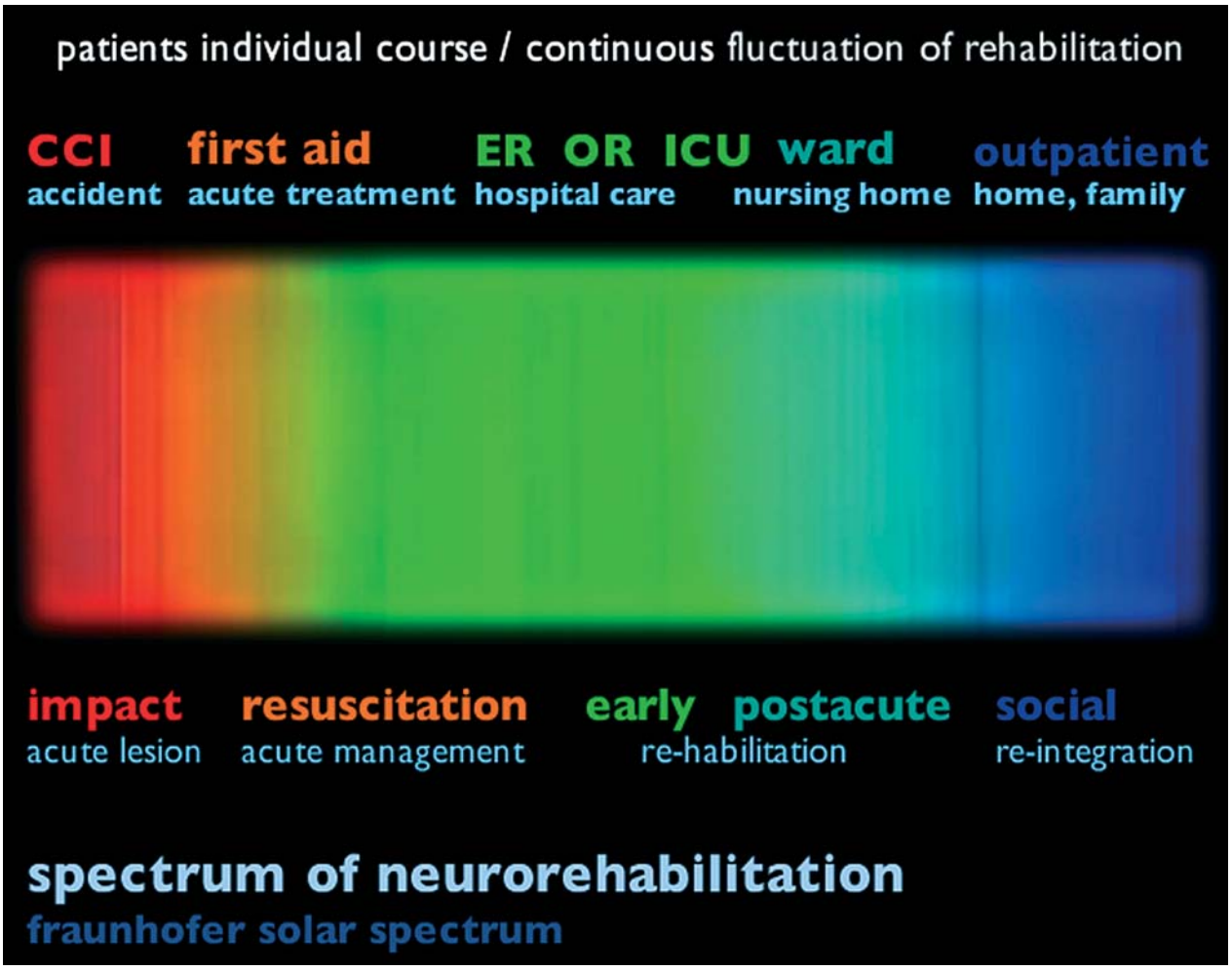

Fig. 1. Spectrum of neurorehabilitation. The patient's process of functional recovery can be seen in analogy to the solar spectrum with its colours and characteristic Fraunhofer lines. CCI patients show also typical landmarks of different phases of recovery over time. Spectrum of neurorehabilitation reflects the interventions for the complex process of holistic functional rehabilitation over time. Rehabilitation starts after the impact to the brain together with first aid and resuscitation at the site of the brain damage. Emergency management and critical care aims at brain protection via restoration and stabilization of ventilation and circulation to prevent secondary hypoxic episodes. Emergency surgery for thoracic, vascular or abdominal lesions go first if of vital importance before operable intracranial haematoma must be evacuated immediately. Intensive-care treatment aims at neuroprotection. This is why early rehabilitation starts at the ICU with assessment of functional impairments for further rehabilitation interventions. The victim is referred as soon as possible for ENNR (phase ''B''), followed by subacute (''B, C'') and long-lasting rehabilitation (''D'') including vocational therapy targeted to reintegrate the victim into family, social life where he or she can enjoy social contacts, job, play, recreation and leisure time, mobility and fun

Patients and methods

The concept of ENNR has been described in detail elsewhere [16, 28, 29]. ENNR interventions require more staff than any other form of rehabilitation [12]. Staffing requirements for 20 patients are calculated as follows: 1 (head) neurosurgeon, 1 (rehabilitation) doctor, and 2 ward assistants if not covered by the central neurosurgical services; 20 (intensive care) nurses, 1½ neuropsychologists, 2 speech and language, 2 physio- and 2 (massage) physical, 4 occupational, and 2 music therapists, 1 social worker, 1 secretary, 1 technical assistant (EEG, EVPs, TCMS, EMG, Doppler, Near-infrared diagnostics) [14, 16, 27, 29]. The classic triad of physical therapy, physiotherapy, and occupational therapy constitute the undisputed basis for motor rehabilitation [8]. Neuropsychological, mental-cognitive, language-speech, and music therapy are becoming ever more critical factors for the patient's final outcome [3, 12]. Social services have the task of psychosocial counselling in economic problems. Electrophysiological diagnostics help to assess impairments (cerebral coma, prolonged unawareness, and minimal consciousness, silent epileptic fits, and recovery of cortical functioning including pharmacological studies [6, 16, 17, 27, 28].

Results

Patients referred for early neurosurgical rehabilitation are those with complex impairments of sensorimotor functioning and/or mental-cognitive, neurobehavioural impairments. Their level of awareness might vary between a certain ''cloudiness'' to severe states of unconsciousness, Apallic Syndrome (AS/VS) (full stage or early remission stage), and coma [9, 22, 26, 27, 29].

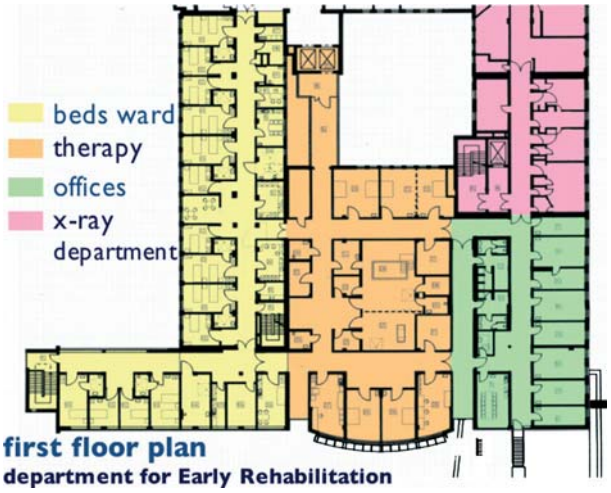

Fig. 2. The authors' specially designed department for ENNR at Clemenshospital. L-shaped ground plan of the ENNR department as part of the neurosurgical clinic where all rooms are located on the first floor (1200 sqm) and connected by short access. Offices to the north, next to the X-ray department, and bed-rooms (single and twin beds, cardiology intensive care style) to the south-east. All necessary therapeutic and diagnostic facilities in the middle next to patients' rooms and two elevators and two staircases

The basic work is done by intensive-care nursing staff [16, 29]. Activating nursing is the fundamental form of therapy in neurosurgical early rehabilitation. Independently from the stage of consciousness and awareness caring procedures and all therapy stages are explained to the patient. With the help of basal stimulation by touching and posturing, the patient's perception of his body and motions in connection with personal hygiene and when being dressed is enhanced in the sense of active daily-living (ADL) training [13, 20, 24, 26]. These measures include the changing of wound dressings, and the laying of gastric tubes, suprapubic urinal catheters, and tracheostoma. Reposturing helps reduce spasticity and enhance the patient's self awareness and sense of his own body, at the same time promoting local blood circulation. Pressure sores and pathological ossifications of the major joints can definitely be prevented by these measures. The rehabilitation management of posturing includes multiple modalities, such as positioning techniques and bringing the patient in an upright and/or a standing position influence arousal reactions and are a highly intensive central acting stimulus. All activities and observations are dutifully documented.

Physical therapy

Body massage is part of classical physical therapy, focussed on relaxing and softening tense muscles of the body and limbs and at the same time stimulating sensorial perception. Locally it increases the blood supply to the cutaneous tissue and prevents pressure sores. The risk of local thrombosis is diminished because of supporting the venous blood backflow. Physical therapy aims at finding strategies to overcome sensory motor impairments.

Tremor, clonus, myoclonic and dystonic crises are clinical signs of specific functional lesions of the cortex and subcortical structures of the brain stem and cerebellum. Brain damage is frequently associated with an increased muscle tone and resultant spasticity and rigidity [8]. Because of his consciousness impairments, the anxious patient might be agitated. Daily warm baths will help the patient to relax and to decrease spastic movement disorders. Without any additional medication spasticity decreases, and the patient will become relaxed, aroused, and positively motivated for the rest of the day. Therapies in the swimming pool are an enormous help in stabilizing the patients' body control and in enabling him to stand and to walk again using the water lift. One will notice here the enjoyment the individual patient derives from personal attention of the physiotherapist.

Physiotherapy

The assessment of impairments of the musculoskeletal system by the doctors and physiotherapists examines the aspects: Is the muscle spastic to passive extension? Does the muscle show increased stiffness when stretched? Does the muscle have fixed shortening? Careful treatment depends on clinical patterns of motor dysfunction in order to identify the best method of treating functional problems as there are: the flexed hip, scissoring thighs, stiff knees, equinovarus foot, bent elbow, pronated forearm, bent wrist, clenched fist, thumb-in-palm deformity. In addition, pharmacological reduction of spasticity can be achieved by local injections of phenol for peripheral nerve blocks and today by the local application of Botulinum toxin, which inhibits the release of actetylcholine causing flaccid paralysis. Both techniques are helpful adjuncts for standard use of casting [15, 16]. Sometimes long-bone and pelvic fractures that are stabilized with the aid of a fixateur externe after polytrauma might hinder nursing, activities of daily living (ADL) [24, 26], physical- and physiotherapeutic interventions [8].

Occupational therapy [16, 19, 24, 29]

Person-to-person devotion is of utmost importance. The daily exercise of practical day-to-day life habits

and activities (ADL) helps the patient to regain a sense of self and to cope with his environment. Functional problems after brain damage are typically caused by spastic phenomena embedded within the impaired selective motor control. Patients in coma or with a minimal responsiveness status manifest rigidity as decerebrate or decorticate posturing. Motor control may be affected at many different functional levels, so that patients present with spasticity and abnormal extension or flexion positioning of the limbs. The purpose of posturing patients in an upright sitting position when emerging from coma or apallic syndrome is to enhance vigilance and cognition by stimulating the ascending system of the reticular formation. The unconscious patient is first treated and mobilized with the aid of a tilting bed for standing. Continuous monitoring of vital signs – for instance systemic blood pressure, heart rate, and cerebral blood perfusion – with the aid of transcutaneous near infrared spectroscopy are helpful [29]. Sitting in an upright position is a strong central stimulus that helps to establish new proprioceptive inputs and to reorganize the vestibular and the central blood-pressure control systems. ADL is performed by occupational therapists in cooperation with nurses, physiotherapists and speech therapists, depending on the nature and severity of the functional impairments involved. The physiological posturing of the patient also plays an important role here. Putting the patient into a standing apparatus for 10–15 minutes helps him to reorganize and to actively train the subcortical autonomous centres for blood pressure, respiration, and heart rate. The benefit of upright positioning is the stimulation of arousal and cognition, and hence the coordination of central motor cortical functions and frontal brain activities. Therefore we check sitting and standing of the patient for assessment of behaviour and cognition with the aid of our CRS [22, 28].

Occupational Snoezel therapy is new and stands for a combined multisensorial stimulation therapy within a special environment [29]. Snoezel helps to arouse and to calm down agitated patients, with the patient himself positioned on a water bed and held tight in the arms of the therapist to feel and to enjoy the physical nearness and warmth. Snoezel aims at the stimulation and treatment of perception disorders: the stimuli applied are tactile, proprioceptive, vestibulary, visual-acoustic, gustatory, and olfactory [12, 13].

Music therapy

Music therapy is based on a neuroscience model of music perception and production and the influence of music on functional changes of emotions and perception in the brain with influence on behaviour functions to neurological disease of the human nervous system [29].

The music therapist aims at reaching the awareness of the patient that cannot be accessed through verbal communication. The music therapist improvises vocally to the breathing of the patient reflecting changes in intensity, tempo, and dynamics. This offers the patient a unique possibility to express his individual self in an expressive musical form. Music therapy on a two-patient basis and in small groups enhances personal and social integration following individuals' isolation and social withdrawal. Recovery of awareness and cognition over time can exemplarily be shown in comatose and apallic patients during recovery.

Neuropsychological therapy

Neuropsychological therapy has become key therapy in ENNR as mental disabilities are both more persistent and constitute a greater handicap than focal neurological signs [2, 3, 12, 16, 18, 29]. Practically all patients after brain damage suffer from impairments of higher integrated cerebral functions. Most of the patients have impairments in alertness and vigilance, problems with memory and learning, and difficulties with abstract reasoning and flexible problem solving. Their capacity to perceive the meaning of ongoing interactions objectively is diminished. In following the treatment concepts of Christensen and Uzzell [3] and Prigatano [18] neuropsychological therapy during early rehabilitation is mainly based on a phenomenological approach [12]. The significance of symptoms and signs can be understood only in the context of the functional system. There is no specific treatment of neglect syndrome, for example secondary to intracranial haemorrhage with left-sided hemiparesis, but general psychological motivation and ease of mind improve over time. The functional system in the brain consists of a number of parts, each being very specific, particularly the cortical one. A preliminary conversation provides information regarding the history, general state, and particular aspects of the patient's mental activity. So we try to provide feedback and to gauge progress and development and, as demonstrated during the treatment of an aphasic patient after ICB, by lending support and modifying the ambient conditions it is possible to encourage the patient when we try to guide his attempts and compensation. Functional training with the aid of personal-computer programmes may be indicated at a certain stage of progress in the restoration of cognition. Self-assessment and feedback is part of the

emotional interaction during psychological treatment. Computer training has become an additional adjunct [12].

Social services

Our social worker turned out to be the main connecting link between the patient's family and hospital affairs complementary to the neuropsychologist, trying to achieve a good quality of life for the patient and the relatives after discharge from hospital.

Brain damage is a family affair [3]. Relatives, therefore, are touched emotionally and socially. They cannot come to terms with the catastrophic situation and are worried about the future. They insist on knowing more about the chance of survival and the functional prognosis. The senior physician informs the family about the functional impairments, risks, and complications, and goes on to explain the design of our therapeutic concept on the basis of careful clinical and psychological assessment. The near and dear become partners of the multidisciplinary team approach for functional recovery and they are included in the daily rehabilitative measures, thus learning how to approach and how to cope with the new situation. The next-of-kin know best the personal structure of the patient from the time before the event, a feature that is prerequisite for individual treatment, and they usually make more detailed observations than do the clinic staff so that they often are the first to register when the comatose patient regains conscious reactions. The next-of-kin are trusted by the patient and especially in the early stage they can help to calm the disoriented and confused patient, thus helping to avoid or reduce vegetative disregulation and while accompanying frightened patients to their therapy sessions they can assist in the stimulation process by taking care of various everyday life activities. The team respects the patient's cultural, religious, and social-economic background. The neuropsychologist and social worker assist here, too, since they are aware of the patient's functional impairment and social background. ''In the beginning, 6 weeks after the traffic accident, the doctors told me that it could be that my daughter Heike, who was in a full stage of apallic syndrome, might be discharged home functionally unchanged if she survived at all, despite all intensive rehabilitation measures that would be taken over the following twelve months. However, they all gave me hope and I was kept informed about her situation at all times!'' patient Heike's father quotes.

Daily visits

The object of the daily visits is to check the state of the patient's health, documenting the functional impairments as well as any improvements in his condition [12, 16, 17, 29]. Even the slightest clinical changes in awareness and motor functions can indicate the progressive recovery of the patient or else an imminent secondary complication, generally involving the respiratory system or of an intestinal, urological, or neurosurgical nature. Intracranial mass lesions and hydrocephalus cause typical neurological and mental-cognitive impairments.

Complications

Respiratory complications and bronchopneumonia are frequent due to swallowing disorders and silent aspiration [6]. The incidence of dysphagia after severe brain damage secondary to TBI and stroke is in the region of 30% [19]. The majority suffer from delayed or totally absent of swallowing responses, with approximately one half showing reduced tongue control and about one-third having reduced pharyngeal transit times and the rest a reduced laryngeal closure, elevation, or spasms. Treatment efforts focus on compensation mechanisms. Video fluoroscopy has become the gold standard for evaluating patients for dysphagia. This method enables the operator to observe the anatomy and physiology of the swallowing mechanism after the bolus administration of barium-impregnated liquid on its way to the oesophagus. The vast majority of patients improve spontaneously [19].

The hospital's X-ray department is next to the ENNR unit (Fig. 2) which is necessary because of frequently required plain films and special radiological diagnostics. Computerized cranial tomography (CCT) has become the gold standard as an imaging diagnostic procedure. Thin-section tomography, vascular imaging, and spinal CT with bone fenestration reveal potential pathological symptoms in the brain, vascular system, ventricular system, and bone structures, also in the region of the base of the cranium. Magnetic resonance tomography (MRT) follow-up studies of the damaged brain allow prognostic prediction [27, 29].

Exclusion criteria for ENNR: All patients with acute brain lesions and suffering from neurological and/or mental cognitive impairments of higher cerebral functioning are eligible for referral to an ENNR department provided they are no longer on the ventilator, sufficiently stable in terms of circulation and breathing, without increased intracranial pressure, and not suffering from severe infection or progressive malignancy nor from progressive cerebral diseases such as M. Alzheimer or Chorea Huntington. All team members meet in weekly rounds to discuss and assess the patients' individual status. Diagnostic findings are presented with comments

on the charts. The performance of sensory motor and cognitive-psychological recovery of functioning is assessed by all team members who are in charge of the patient over weeks and months.

Cut-off points

The functional impairment and fluctuation is best mirrored with the aid of the coma remission scale score. A score of 24 points on the 24 points CRS [16, 28, 29] in conjunction with ERBI $>+40$ points [20] constitute the cut-off criterion.

No patient with less than 20 points on day 40 reached a functional outcome of the Glasgow outcome scale score 4 or 5, no patient with fewer than 10 points emerged from apallic syndrome within one year.

Time interval (see Table 1) between head injury and the start of neurorehabilitation was less than one month for 175 TBI ($=67.2\%$) and one to three months for 60 patients while average time of stay for ENNR ''B'' was 58 days (1–366 days) and for postacute ''C'' 41 days (2–300 days) respectively according to the prospectively controlled study on TBI management in Germany [29].

Functional outcome [7, 29] and quality of life [25] (Fig. 1) after some years of two of our patients which is in accordance with the results obtained in the prospective study of 6800 acute TBI [29] confirm our concept for ENNR exemplarily. Case 1: Three years ago a young lady, a student of chemistry, experienced a severe CCI of the GCS 3 category followed by an apallic syndrome lasting over nine months. Now she lives on her own in a specially equipped environment for handicapped people.

Table 1. *Time interval and frequency of TBI patients admittance for ENNR (N = 100)*

Interval/ days	MS	MS and other hospitals	H	Other hospitals	*N*	(%)
1–7	16	2	0	1	19	19.0
8–14	9	4	2	2	17	17.0
15–21	15	3	5	2	25	25.0
22–30	7	3	4	7	21	21.0
30–90	5	0	5	7	17	17.0
91–180	0	0	0	1	1	1.0
Patients (%)	52	12	16	20	100	100.0

Time interval between acute brain damage in respect to the primary hospital that referred the TBI patient for ENNR. MS = same (author's) hospital as neurosurgical rehab unit, MS and other hospitals include second neurosurgical department Münster without unit for ENNR and other hospitals in the Münster area; *H* admission from two neurosurgical departments of Hannover area, other hospitals = rest of hospitals of the Hannover region. Data from the prospective study on quality management of TBI in Hannover and Münster regions 2000/2.

Her beloved best friend is her horse from earlier times, when she went for competitions. Three times a week she goes for horseback riding. Her teacher said that she has constantly improved her sensorimotor, vestibular, and cognitive behavioural functioning. Case 2: Two years ago, one gentleman was twice virtually dead because of severe brainstem haemorrhage. He was in coma and mechanically ventilated for two weeks, gradually making a slow recovery during early rehabilitation two years before. Now back at his normal environment again, he enjoys his family, home, horses, leisure time, and the beautiful landscape. He enjoys his social reintegration and visits his factory twice a week. A young male nurse takes care of his active daily living and has become his chauffeur for the new Daimler. Although partly disabled, this man and his family are entirely happy with the functional result and his mobility.

Discussion

In Germany roughly 6000 people die as a consequence of traffic accidents each year, 2500 as a direct result of traumatic brain injury. Year by year, 260,000 patients are admitted to German hospitals for the treatment of traumatic brain injury (TBI). Of this total, about 5% suffer from the severest forms, 10–15% from a more moderate form, and most patients from so-called mild TBI. Stroke shows exactly the same incidence of 320 per 100,000 population. In respect to the consequences of the severest form of brain damage the prevalence of an Apallic Syndrome (AS)/VS secondary to traumatic and nontraumatic brain lesions, as reported in the international literature, ranges widely, for Europe 0.5 to 2.0/100,000 population. Recently Stepan *et al.* reported objective figures of 1.7 per 100,000 population for Vienna, the capital of Austria, with 1,620,170 population at the time of analysis (Nov. 2003) which are based on their personal examination of patients with AS and expertise in AS diagnostics and treatment [22]. Recovery from AS is defined as the ability to establish visual or verbal contact with the outside world. The AS recovery rate is reported to be mainly dependent on age when children do better (about 70%) than adults (45–50%) and on the primary impact to the brain when patients with cerebral hypoxemia secondary to cardiac arrest, strangle, and near-drowning or hypoglycaemic intoxication after resuscitation do worst. Most patients who regained consciousness did so in the first 3 months. After one year only some few

of the AS patients may achieve some minimal responsiveness and early stage of functional recovery or they remain in AS full stage. Techniques of FES (functional electrical stimulation) are not yet routinely applied in our department, although there is clear evidence of safety and effectiveness as reported by Kanno for his dorsal column spinal cord stimulation (DCS) [10, 11, 14], by Tsubokawa *et al.* for deep-brain stimulation [23, 30], and for Edwin B Cooper's right median nerve electrical stimulation [4] to hasten awaking from coma and AS/VS.

Functioning in the sense of WHO-ICF is an umbrella term encompassing all body functions, activities and participation taking into account all the physical, neurological and mental-cognitive impairments. Quality of life (QoL) [1] is accordingly mirrored by the impairments that refer to loss of structures and functions, while disabilities refer to limitations or participating restrictions (Fig. 1) [25]. Our data on the epidemiology and quality management of ENNR [29] met the criteria set in 1993 [12, 16, 28]. Management of frequent multiple organ lesions and complications (= 57%) without referring the patient to another hospital [5, 6, 29] and early functional outcome [7, 25, 29] confirm the authors' concept of neurosurgical early rehabilitation.

Aknowledgement

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References

1. Berger E, Leven F, Pirente N, Bouillon B, Neugebauer E (1999) Quality of life after traumatic brain injury: a systematic review of the literature. Rest Neurol Neurosc 14: 93–102
2. Ben-Yishay Y, Daniels-Zide E (2000) Examined lives: Outcome after holistic rehabilitation. Rehabilitation Psychology 45(2): 112–129
3. Christensen A-L, Uzzell BP (1988) Neuropsychological rehabilitation. Kluwer Academic Publishers, Boston, Dorfdrecht, London
4. Cooper JB, Jane JA, Alves WM, Cooper EB (1999) Tight median nerve electrical stimulation to hasten awaking from coma. Brain Injury 4: 261–267
5. Groswasser Z, Cohen M, Blankstein E (1990) Polytrauma associated with traumatic brain injury: Incidence, nature and impact on rehabilitation outcome. Brain Injury 4(2): 161–166
6. Hoffmann B, von Wild KRH (2001) Incidence and management of complications during posttraumatic early rehabilitation. Acta Neurochir [Suppl] 79: 25–29
7. Hoffmann B, Düwecke C, von Wild KRH (2001) Neurological and social long-term outcome after early rehabilitation following traumatic brain injury. Five-year report on 240 TBI patients. Acta Neurochir [Suppl] 79: 37–39
8. Hömberg V (2005) Evidence-based physical therapy. A critical review. Acta Neurochir [Suppl] 93: 3–14
9. Jennett B (2002) The vegetative state. Cambridge University Press, UK
10. Kanno T, Kamei Y, Yokoyama T *et al* (1987) Neurostimulation for patients in vegetative status. PACE 10: 207–208
11. Kanno T, Okuma I (2003) Electrical neurostimulation for vegetative state. Proceedings of the 12th Annual Meeting of the Society for Treatment of Coma 12: 3–7
12. Kemper B, von Wild KRH (2001) Requirements for team effectiveness in neurosurgical rehabilitation. Acta Neurochir [Suppl] 79: 37–39
13. Müller SV *et al* (2002) The effects of proprioceptive stimulation on cognitive processes in patients after traumatic brain injury. Arch Phys Med Rehabil 83: 115–121
14. Okuma I, Onouchi K, Yamaguchi S *et al* (2003) Examination of regional eCBF (cerebral blood flow) in PVS (persistent vegetative state) with 3DSRT (3-dimensional stereotaxic region of interest template) – preliminary report. Proceedings of the 12th Annual Meeting of the Society for Treatment of Coma 12: 9–17
15. Ortega-Suhrkamp E (2001) Early functional outcome in isolated (TBI) and combined traumatic (CTBI) brain injury. Acta Neurochir [Suppl] 79: 31–32
16. Ortega-Suhrkamp E, von Wild KRH (2002) Standards of neurological-neurosurgical rehabilitation. Acta Neurochir [Suppl] 79: 11–19
17. Pagni CA (2005) Posttraumatic epilepsy. Acta Neurochir [Suppl] 93: 113–119
18. Prigatano GP (1999) Principles of neuropsychological rehabilitation. Oxford University Press, Oxford, New York
19. Prosiegel M, Höling R, Heintze M *et al* (2005) Swallowing therapy – a prospective study on patients with neurogenic dysphagia due to unilateral paresis of the vagal nerve, Avalli's syndrome, Wallenberg's syndrome, posterior fossa tumours and cerebellar hemorrhage. Acta Neurochir [Suppl] 93: 35–37
20. Schönle PW (1996) Frühe Phasen der neurologischen Rehabilitation. Differentielle Schweregradbeurteilung bei Patienten in der Phase B (Frührehabilitation) und in der Phase C (Frühmobilisation/postprimäre Rehabilitation) mit Hilfe des Frühreha-Barthel-Index (FRBI). Neurol Rehabil 1: 21–25
21. Stein DG (2000) Brain injury and theories of recovery. In: Christensen AL, Uzzell BP (eds) International handbook of neuropsychological rehabilitation, pp 9–32
22. Stepan Ch, Haidinger G, Binder H (2004) Prevalence of persistent vegetative state/apallic syndrome in Vienna. Eur J Neurol 11: 461–466
23. Tsubokawa T, Yamamoto T, Katayama Y *et al* (1990) Deep-brain stimulation in a persistent vegetative state: Follow up results and criteria for selection of candidates. Brain Injury 4: 315–327
24. Voll R, Krumm B, Schweisthal B (2001) Functional independence measure (FIM) assessing outcome in medical rehabilitation of neurologically ill adolescents. Int J Rehabil Res 24: 123–131

25. von Steinbüchel N (2005) Assessment of health-related quality of life in persons after traumatic brain injury – development of the QOLIBRI, as specific measure. Acta Neurochir [Suppl] 93: 43–49
26. Wade DT (1992) Measurement in neurological rehabilitation. Oxford Univ Press, Oxford
27. von Wild KRH, Simons P, Schoeppner H (1992) Effects of pyritinol on EEG and SSEP in comatose patients in the acute phase of intensive care therapy. Pharmacopsychiatry 25: 157–166
28. von Wild KRH (2000) Perioperative management of severe head injuries in adults. In: Schmidek H (ed) Operative neurosurgical techniques: indications, methods, and results. Saunders Company, Philadelphia, pp 45–60
29. von Wild KRH (2005) Neurorehabilitation following craniocerebral trauma. Eur J Trauma 4: 344–358
30. Yamamoto T, Katayama Y, Kobayashi K *et al* (2003) DBS therapy for persistent vegetative state: Ten-year follow-up results. Acta Neurochir [Suppl] 87: 15–18

Addendum

Coma Remission Scale (CRS)

GERMAN TASK FORCE ON

Neurological-Neurosurgical
Early Rehabilitation 1993 [28]

Patient name:

Date:	
Investigator (initials):	

1. Arousability/attention (to any stimulus)

Attention span for 1 minute or longer	5	
Attention remains on stimulus (longer than 5 sec)	4	
Turning towards a stimulus	3	
Spontaneous eye opening	2	
Eye opening in response to pain	1	
None	0	

2. Motoric response (minus 6 points from max. attainable sum if tetraplegic)

Spontaneous grasping (also from prone position)	6	
Localized movement in response to pain	5	
Body posture recognizable	4	
Unspecific movement in response to pain (vegetative or spastic pattern)	3	
Flexion in response to pain	2	
Extension in response to pain	1	
None	0	

3. Response to acoustic stimuli (**e.g. clicker**) (minus 3 points from max. attainable sum if deaf)

Recognizes a well-acquainted voice, music, etc.	3	
Eye opening, turning of head, perhaps smiling	2	
Vegetative reaction (startle)	1	
None	0	

4. Response to visual stimuli (minus 4 points from max. attainable sum if blind)

Recognizes pictures, persons, objects	4	
Follows pictures, persons, objects	3	
Fixates on pictures, persons, objects	2	
Occasional, random eye movements	1	
None	0	

5. Response to tactile stimuli

Recognizes by touching/feeling	3	
Spontaneous, targeted grasping (if blind), albeit without comprehension of sense	2	
Only vegetative response to passive touching	1	
None	0	

6. Speech motor (logomotor) response (tracheostoma = 3 if lips can be heard to utter guttural sounds/seen to mime "letters")

At least one understandably articulated word	3	
Unintelligible (unarticulated) sounds	2	
Groaning, screaming, coughing (emotional, vegetatively tinged)	1	
No phonetics/articulation audible/recognizable	0	

Sum score:		
Max. Attainable score (of 24) for this patient		

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Involuntary movement disorders

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Deep brain stimulation as a functional scalpel

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Summary

Since 1995, at the Istituto Nazionale Neurologico ''Carlo Besta'' in Milan (INNCB,) 401 deep brain electrodes were implanted to treat several drug-resistant neurological syndromes (Fig. 1). More than 200 patients are still available for follow-up and therapeutical considerations. In this paper our experience is reviewed and pioneered fields are highlighted.

The reported series of patients extends the use of deep brain stimulation beyond the field of Parkinson's disease to new fields such as cluster headache, disruptive behaviour, SUNCt, epilepsy and tardive dystonia.

The low complication rate, the reversibility of the procedure and the available image guided surgery tools will further increase the therapeutic applications of DBS. New therapeutical applications are expected for this functional scalpel.

Keywords: Deep brain stimulation; movement disorder; chronic pain; dystonia; Parkinson's disease.

Introduction

At the beginning of the century stereotactic neurosurgery was used on animals for experimental purpose with the aim of mapping the brain's electrical activity and functional responses. The mapping process was followed by the development of surgery that was capable of changing function of brain, through small lesions in a ''key'' area. In the nineties, deep brain stimulation (DBS), after its optimization by Benabid [2–5], for the control of parkinsonian tremor gained worldwide the role of a promising therapeutical tool. The administration of high frequency and low amplitude electric stimulation, allows the modulation of neuronal activity in a reversible way: the parameter of stimulation can be adapted according to the clinical response. Nevertheless the way DBS works is still unclear. More experimental data are required to understand whether the interaction with the neurological functions is obtained through the inhibition or the activation of cellular activity which modulates the output of specific neural networks. There is interest, moreover, to investigate new targets in order to find new therapeutical applications to approach otherwise untreatable diseases. The development of computer-based workstations allows the use of multimodality image sets for the surgical planning, while neuroimaging provides a functional scalpel and a powerful research tool in the hand of the neurosurgeon. Since 1995 at Istituto Nazionale Neurologico ''Carlo Besta'' in Milan (INNCB), 401 deep brain electrodes were implanted to treat several drug-resistant neurological syndromes (Fig. 1). More than 200 patients are still available for follow-up and therapeutical considerations. In this paper our experience is reviewed and pioneered fields are highlighted.

Patients and methods

Movement disorders

Parkinson's disease: The long term results of 85 parkinsonian patients submitted to bilateral stereotactically guided implant of electrodes into the subthalamic nucleus (STN) are available. Mean age 55.7 ± 7.7 yrs, duration of the disease 11.9 ± 4.2 yrs, follow-up 25.4 ± 16.7 yrs. UPDRS motor score were of 55.1 ± 14.8 in off-drug and 19.0 ± 11.0 in on-drug.

The present series extends to the long-term observation ($FU > 12$ months) of our previous follow-up [6, 7]. Eight more patients affected by dopa-related diskinesias underwent Gpi neurostimulation.

Tremor: twelve patients underwent Voa-Vop-Zi high frequency stimulation (HFS). Four patients were affected by multiple sclerosis (MS), three patients by posttraumatic tremor, and five patients Parkinsonian tremor. Four patients affected by essential familial tremor, underwent Vim (HFS).

Dystonia: twenty-eight dystonic patients underwent Gpi HFS. This series include patients affected by primary dystonia DYT 1−, DYT 1+ (only one patient) and symptomatic dystonia (including three cases of drug induced tardive dystonia). Onset of symptoms ranged between

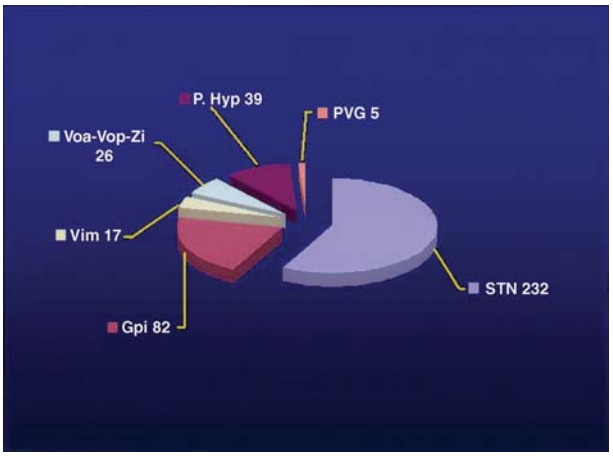

Fig. 1. Graphic representation of the whole series of deep brain electrodes implanted since 1995 at the neurological institute "C. Besta", Milan (*stn* subthalamic nucleus, *GPi* globus pallio pars interna, *Vim* ventralis intermediate nucleus, *Voa-Vop-Zi* ventral oralis ventral posterior and zona incerta, *P. Hyp* posterior hypothalamus, *PVG* periventricular grey)

2 and 50 years of age. Duration of the disease at the time of surgery ranged between 4 and 30 years. Preoperative and postoperative evaluation included video recording and assessment of dystonia with Burke-Fahn-Marsden Dystonia Rating Scales (BMFDRS).

Chronic pain

Posterior medial hypothalamic stimulation has been performed in 16 patients with chronic Cluster Headache (CH), one patient with short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT), and three patients with neurogenic facial pain.

Disruptive behaviour

Posterior medial hypothalamic stimulation has been performed in two patients with major psychorganic diseases and disruptive behaviors, all patients were institutionalized and required continuous sedation.

Epilepsy

Chronic stimulation of the posteromedial portion of the substantia nigra has been performed in one young female (age 26) suffering from disabling posttraumatic drug resistant partial motor seizures (more than 100 seizures per month).

Surgical technique

Today different imaging modalities are available to calculate the target position coordinates by direct visualization of anatomical structures and by indirect calculations based on the commissural reference system. Even if the approach to planned target is more accurate than several years ago, many factors may lead to an error in the final position of the electrode (e.g. MRI distortion and individual variability). So microrecording of neuronal activity and micro-macrostimulation is still helpful. The introduction of this peroperative neurophysiological investigation has improved the safety and accuracy of functional neurosurgical procedures.

The day before surgery we perform accurate planning by imaging. MRI (T1 and fast spin echo inversion recovery sequences with double dose of contrast-agent) is used to obtain high definition anatomical images of the intercommissural plane, allowing the calculation of the midcommissural point coordinates. MR images are merged with computed tomography (CT) images obtained stereotactically (CRW or Leksell frame) through a dedicated workstation (Stealth Station Treon SofamorDanek, Medtronic Inc. Minneapolis/US). The stereotactic coordinates of the chosen target are obtained within the virtually built 3D space enriched by vessels enhancement. The planning of the target is refined comparing the results obtained by the workstation with a dedicated software developed at our Institute (Virtualventriculography, Solaris), which is a self learning atlas based on the statistical analysis of previous implants. In this way the targeting procedures may take advantages from a probabilistic functional stereotactic atlas (Fig. 3).

a

GPi	x	±19
	y	2
	z	-6

b

STN	x	±12
	y	-4
	z	-4

c

Zi	x	±15
	y	-7
	z	-4

d

SN	x	±10
	y	-7
	z	-6

e

Hypothalamus	x	2
	y	-3
	z	-5

Fig. 2. Target coordinates registered to the AC-PC midpoint: (a) Dystonia; (b) Parkinson's disease; (c) tremor; (d) epilepsy; (e) cluster headache and aggressive behaviour

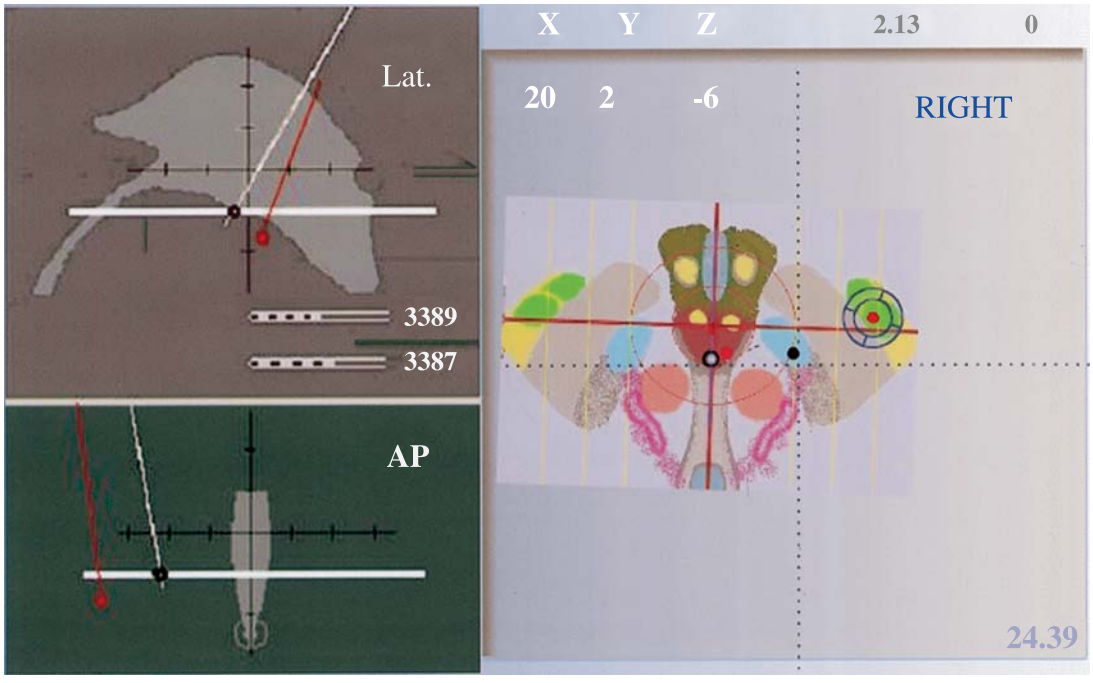

Fig. 3. Snapshot of the virtual ventriculography program (Wandor software, Dolgo, PC, Italy) showing the plate 6 mm below the commissural plane. The trajectories to the GPi (red) and STN (black) nuclei are represented on the ventricles AP and lateral profile. Targets are represented on the corresponding axial section (green: GPi, yellow: optic tract, cyan: STN, dark dotted grey: substantia nigra, pale grey: internal capsula, pink red nucleus, dotted violet: sensory lemniscal fibres)

Most of the procedures have been performed through a 7 mm precoronaric paramedian burr hole. Microrecording is used for the neurophysiological confirmation of the target in Parkinson's disease. Micro and/or macrostimulation has been performed in all procedures to rule out the adverse effects induced by electrical current delivered at therapeutical levels.

All the procedures were conducted in local anaesthesia except for generalized dystonia where general anaesthesia without curarization was preferred. Patients in general anaesthesia underwent only macrostimulation to establish the motor threshold avoiding implants too close to the internal capsule.

The individual variability of the target along the anteroposterior axis due to the high individual variability of the midbrain angle is considered and corrected in all the procedures below the commissural plane. In these cases a third point 8 mm below the commissural plane is considered to correct the AC-PC registered system. To verify the position of the electrode, CT was always performed after stereotactic surgery but before the pulse

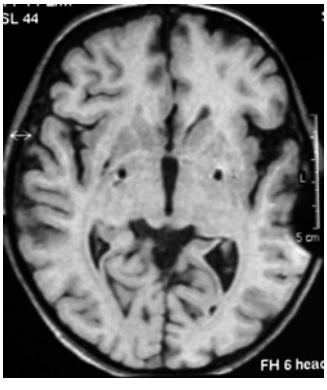

Fig. 4. Postoperative MRI merged with the preoperative MRI planning showing electrode position (T1 weighted images)

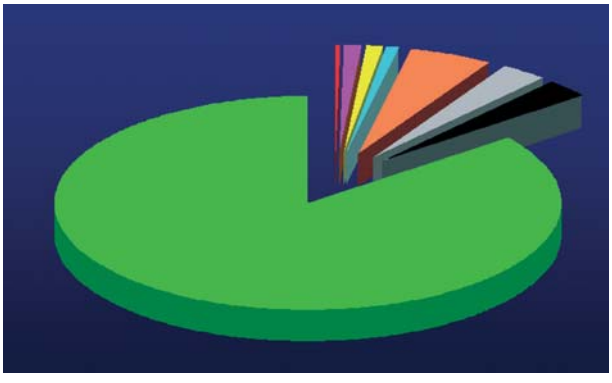

Fig. 5. Graphic representation of the complications (red: hemorrhage; violet: permanent neurological deficits, yellow: transient neurological deficits, cyan: postoperative seizures, brown: hardware removal, grey: hardware failure, black: electrodes migration, green: no complications)

generator was placed. This examem is merged with the preoperative planning in order to verify the electrode position [11] (Fig. 4).

Results

Movement disorders

Parkinson's disease: At a follow-up of 25.4 ± 16.7 months UPDRS in off-drug with stimulation is 26.4 ± 11.7, while in on-drug with stimulation is 15.4 ± 9.1. The variation off/off+ stimulation is -52.1% and variation on/on $+$ stimulation is -19.1%.

Dystonia: All patients showed a clinical improvement, as evaluated by the BMFDRS scales, that ranged between 27 and 88%. The improvement was progressive over a period of 3–6 months after surgery, and persisted during the follow-up (4–48 months). Our results demonstrate that DBS is an effective treatment for dystonia, with no remarkable side effects, even in childhood. In tardive dystonia the results are higher than 90% with immediate effects.

Tremor: All patients regained autonomous self feeding and personal care at 12–36 months follow-up with continuous high frequency stimulation. All Vim, Voa-Vop-Zi targets showed efficacious results but the latter allowed a better control of the ataxic component.

Chronic pain

Cluster headache: At four years follow-up the percentage of the total number of days free from pain attacks improved from up to 78% and 10 patients of this series had a complete and persistent pain-free state.

SUNCT: At 18 months follow-up the patient had complete pain relief.

Neurogenic facial pain: Neurostimulation procedure was absolutely unsuccessful.

Disruptive behaviour

Stable improvement with a 12 months follow-up was obtained and a marked reduction in sedative drugs was achieved allowing us to stop the contentive hospital procedures.

Epilepsy

At 15 months follow-up the only operated patient reported a 60% dramatic reduction of seizures.

Complications

Massive brain haemorrhage occurred in one case of STN implant (0.4%); permanent neurological deficits due to deep haemorrhage occurred in four patients of which one was a Vim implant and the other STN implants (1%). Transient neurological deficits due to deep haemorrhage occurred in five patients (1.2%); postoperative seizures occurred in three patients (0.7%); hardware removal due to infection occurred in twenty-two cases (5.4%) one of which had cerebral abscess at the origin of the stereotactic trajectory; hardware failure occurred in twelve patients (2.9%); late electrode migration occurred in twelve patients (2.9%) of which eight were under fourteen years old.

Risk rate is referred to single electrode implant surgery, patients who need more than one electrode implant may expect a higher risk rate.

Discussion

Movement disorders

Parkinson's disease: As far as the field of movement disorders is concerned, advanced Parkinson's disease remains the main indication for DBS. Drug treatment of parkinsonian symptoms unfortunately cannot avoid disability in an advanced course of disease since long-term levodopa therapy often results in invalidating motor fluctuations and dyskinesias. In the 1980s, the side effects and limits of chronic L-dopa therapy became obvious and led to reintroduction of the surgical treatment of motor symptoms in Parkinson's disease (PD). Advances in stereotactic surgery, neuroimaging [15, 16], electrophysiologic recordings and the possibility to obtain therapeutic responses by high-frequency deep brain stimulation (DBS) have renewed interest in the surgical treatment of PD. During the last 10 years, several groups have demonstrated that chronic DBS of the VIM, subthalamic nucleus (STN), or globus pallidus internus is an effective treatment for disabling pharmacotherapy-resistant motor symptoms (tremor, rigidity, bradykinesia) in PD. Increasingly evidence in favour of the subthalamic nucleus (STN) as the target of choice has been collected [4–6]. The experimental data in MPTP monkeys along with clinical results in human PD patients after both STN lesion or high frequency stimulation, point toward a major role of STN hyperactivity in the pathophysiology of PD. Deep brain stimulation seems to produce a functional inhibition of the neurons in the targeted structure that mimics the result

of lesioning. The main advantage of this procedure versus lesioning is related to the reversibility and adjustability of its effects without any cerebral permanent damage. The parameters of stimulation can be changed to increase efficacy or to reduce side effects. In the future a more oriented choice between the available targets (Vim-Zi-STN-Gpi-CM) will further improve clinical outcome.

Dystonia: Dystonia is a neurological syndrome characterized by abnormal postures and involuntary movements.

The physiopathologic basis of dystonia has not yet been completely clarified, however, the cortical-subcortical network and the globus pallidus internus (Gpi) are the structures primarily involved. Pharmacological treatment of dystonia is sometimes disappointing.

The practice of lesioning in dystonic patients was very common in the 1950s and 1960s, since at that time it was essentially the only available treatment for severe cases. These procedures, performed 50 years ago, were reported to have results not always satisfying, sometimes with severe side effects. By the 1980s, brain surgery for dystonia was abandoned. However, the increased understanding of the pathophysiology of movement disorders and the availability of DBS technology led to a resurgence of interest in the surgical treatment of dystonia; with globus pallidus internus (GPi) still the favourite target [9, 13, 21]. The timing of clinical improvement observed in dystonia is different from that observed in Parkinson's disease. In fact, days, weeks and most often months are required and, moreover, the improvement continues for years, suggesting a phenomenon of neuronal plasticity rather than a simple transitory functional inhibition of a pool of neurons.

Tardive dystonia (TDt) affects about 15% of patients treated by long term neuroleptics therapy and has the potential of becoming irreversible and untreatable in 1–4% of these patients. According to results from literature, when drug therapy is ineffective, thalamotomy can be applied with good but sometimes transient results. Side effects such as dysarthria, dysphonia, and motor disturbances have been described, particularly when thalamotomy is bilateral. The three patients we selected for surgical treatment presented with the typical features of drug resistant TDt: they were young males, TDt onset was observed after a long period of neuroleptics treatment, dystonia persisted after withdrawal of the causative drug with resistance to any medical treatment. Tottemberg [20] was the first surgeon to use DBS for TDt: he investigated the effect of two different targets, VIM and GPi, on the same patient. While VIM did not result in any improvement of movement control, GPi did. Therefore, we treated our patients with bilateral GPi high frequency stimulation. Stimulation started the first day after surgery and immediate improvement could be obtained, differently from what can be generally observed in dystonia of different origin. In our TDt patients neuroleptic drug administration was not discontinued: GPi neurostimulation was found to act as a sort of protection against this particular drug related side effect. High frequency chronic GPi stimulation was found to be safe, highly and promptly effective in these patients, and GPi stimulation has the potential to become the elective treatment of TDt, however these results has to be validated by larger series.

Tremor: The impressive reduction of tremor obtained either immediately during the surgical procedure or at long term follow-up in Parkinson's disease, lead to propose neurostimulation as a suitable treatment of symptomatic tremor in multiple sclerosis patients. The first reported cases of midbrain electrical stimulation on multiple sclerosis patients (MS) with ataxic tremor were reported by Brice and Mc Lellan in 1980. The four patients of our preliminary series were selected on the basis of major impairment provoked by intentional and at rest upper limb tremor. These findings raise the possibility that ataxic tremor could benefit from chronic high frequency Voa-Vop-Zi electrical stimulation.

Pain

Pain represents one of the most challenging issues for neurosurgeons. DBS and other neuromodulation procedures may offer a valid alternative to ablative procedures, which always produce a permanent damage that sometimes can give rise to neuropathic pain. Cluster headache (CH) in particular has been the first indication in the field of chronic pain: it was recognized starting from metabolic and functional neuroimaging which pointed to the postero medial hypothalamus. CH is a painful syndrome of the face often characterized also by symptoms of more general hypothalamic involvement such as psychomotor agitation. Recent imaging studies (PET and fMRI) demonstrated hypothalamic asymmetry and activation during pain attacks [13, 14, 19]. In line with these studies, suggesting the hypothalamus as the origin of pain attacks, we tried to interfere with the supposed hypothalamic hyperactivity through DBS.

Disruptive behaviour

Aggressive behaviour may be associated with different psychotic diseases and/or severe oligophrenic con-

ditions. Control of aggressiveness in most cases may be obtained by drugs including phenothiazines and neuroleptics. Nevertheless, in selected cases, control of aggressive behaviour may be problematic due to the need of high dosages of drugs producing major side effects and sedation, which made caring for these patients even more distressing. In the sixties several neurosurgical procedures have been proposed and performed to treat the aggressiveness in psychotic patients, but the danger of irreversible lesions to CNS structures involved in the control of cognitive functions and mood put such surgery in conflict with ethics. Also, electroconvulsive therapy (ECT) was progressively decried in the seventies due to evidence of irreversible brain damage inflicted by repeated procedures. On the other hand, the last three decades have provided a huge amount of data and knowledge about the neurophysiological mechanisms of aggressive behaviour since the first experience of Delgado on animals with neurostimulators implanted in the limbic system. Since the last decade the Delgado experience and similar experimental studies have inspired more science fiction writers than neurosurgeons.

Bilateral stereotactic lesion of the posteromedial hypothalamus was first reported by Sano in the sixties. This kind of surgery, also known as sedative neurosurgery, found little diffusion for fear of irreversible effects. Our recent experience of chronic hypothalamic stimulation for the treatment of intractable cluster headache demonstrated the feasibility and safety of this procedure and renewed our interest in this target. Deep brain stimulation (DBS) of the posterior hypothalamus was then performed in two patients [13]. DBS of the posterior hypothalamus could lead to a resurgence of interest in the treatment of severe behavioural disorders.

Epilepsy

Although surgical resection of the seizure focus is the treatment of choice of refractory epilepsy, DBS may be an alternative procedure when the focus involves eloquent, unresectable areas. Stimulation of different brain structures such as the cerebellum (Cooper *et al.* 1973), the locus coeruleus (Faber and Vladyka, 1983), the thalamic centromedian nucleus (Velasco *et al.* 2000) and the STN-SN (Benabid *et al.*) has been effective in reducing seizure rate in humans [1, 9, 11, 17]. Several experimental data strongly suggested that basal ganglia and striatal pathways are involved in epileptic seizures threshold and diffusion.

Our results obtained in a young patient (26 yrs) submitted to DBS procedure of the SN-pars posteromedialis. Confirm the literature data and support application of DBS for the treatment of rolandic post-traumatic seizures.

Conclusions

The reported series of patients extend the use of DBS beyond the field of PD to new fields such as cluster headache, distruptive behaviour, SUNCT, epilepsy and tardive dystonia.

The low complication rate, the reversibility of the procedure and the available image guided surgery tools will further increase the therapeutic applications of DBS. New therapeutical applications are expected for this functional scalpel.

References

1. Benabid AL, Minotti L, Koudsie A, de Saint Martin A, Hirsch E (2002) Antiepileptic effect of high-frequency stimulation of the subthalamic nucleus (corpus luysi) in a case of medically intractable epilepsy caused by focal dysplasia: a 30-month follow-up: technical case report. Neurosurgery 50: 1385–1391
2. Benabid AL, Benazzouz A, Hoffmann D, Limousin P, Krack P, Pollak P (1998) Long-term electrical inhibition of deep brain targets in movement disorders. Mov Disord 13 [Suppl] 3: 119–125
3. Benabid AL, Pollak P, Gervason C, Hoffmann D, Gao DM, Hommel M, Perret J, de Rougemont J (1991) Long-term suppression of tremor by chronic stimulation of the ventral intermediate thalamic nucleus. Lancet 337: 403–406
4. Benabid A, Koudsie A, Benazzouz A, Fraix V, Ashraf A, Le Bas JF, Chabardes S, Pollak P (2000) Subthalamic stimulation for Parkinson's disease. Arch Med Res 31: 282–289
5. Benabid AL, Pollak P, Gross C, Hoffmann D, Benazzouz A, Gao DM, Laurent A, Gentil M, Perret J (1994) Acute and long-term effects of subthalamic nucleus stimulation in Parkinson's disease. Stereotact Funct Neurosurg 62: 76–84
6. Broggi G, Franzini A, Marras C, Romito L, Albanese A (2003) Surgery of Parkinson's disease: inclusion criteria and follow-up. Neurol Sci 24 [Suppl] 1: S38–S40 (review)
7. Broggi G, Franzini A, Ferroli P, Servello D, D'Incerti L, Genitrini S, Soliveri P, Girotti F, Caraceni T (2001) Effect of bilateral subthalamic electrical stimulation in Parkinson's disease. Surg Neurol 56(2): 89–94; discussion 94–96
8. Chabardès S, Kahane P, Minotti L, Koudsie A, Hirsch E, Benabid AL (2002) Deep brain stimulation in epilepsy with particular reference to the subthalamic nucleus. Epileptic Disord 4 [Suppl] 3: 83–93
9. Coubes P, Roubertie A, Vayssiere N, Hemm S, Echenne B (2000) Treatment of DYT1-generalised dystonia by stimulation of the internal globus pallidus. Lancet 355: 2220–2221
10. Dinner DS, Neme S, Nair D *et al* (2002) EEG and evoked potential recording from the subthalamic nucleus for deep brain stimulation of intractable epilepsy. Clin Neurophysiol 113: 1391–1402
11. Ferroli P, Franzini A, Marras C *et al* (2004) A simple method to assess accuracy of deep brain stimulation electrode placement: pre-operative stereotactic CT+ postoperative MR image fusion. Stereotact Funct Neurosurg 82: 14–19
12. Franzini A, Marras C, Ferroli P, Bugiani O, Broggi G (2005) Stimulation of the posterior hypothalamus for medically intractable impulsive and violent behavior. Stereotact Funct Neurosurg 83(2–3): 63–66

13. Franzini A, Marras C, Ferroli P, Zorzi G, Bugiani O, Romito L, Broggi G (2005) Long-term high-frequency bilateral pallidal stimulation for neuroleptic-induced tardive dystonia. Report of two cases. J Neurosurg 102(4): 721–725
14. Franzini A, Ferroli P, Leone M, Broggi G (2003) Stimulation of the posterior hypothalamus for treatment of chronic intractable cluster headaches: first reported series. Neurosurgery 52(5): 1095–1099; discussion 1099–1101
15. Kondziolka D, Dempsey P, Lunsford L, Kestle JRW, Dalan EJ, Kanal E, Tasker RR (1992) A comparison between magnetic resonance imaging and computed tomography for stereotactic coordinate determination. Neurosurgery 35: 696–704
16. Kondziolka D, Flickinger J (1996) Use of magnetic resonance imaging in stereotactic surgery. Stereotactic Funct Neurosurg 66: 193–197
17. Loddenkemper T, Pan A, Neme S (2001) Deep brain stimulation in epilepsy. J Clin Neurophysiol 18: 514–532
18. Lozano AM, Hutchison WD, Dostrovsky JO (1995) Microelectrode monitoring of cortical and subcortical structures during stereotactic surgery. Acta Neurochir [Suppl] 64: 30–34
19. Sano K, Sekino H, Hashimoto I, Amano K, Sugiyama H (1975) Posteromedial hypothalamotomy in the treatment of intractable pain. Confin Neurol 37(1–3): 285–290
20. Tottemberg T, Paul G, Meissner W *et al* (2001) Pallidal and thalamic neurostimulation in severe tardive dystonia. J Neurol Neurosurg Psychiatry 70: 557–559
21. Zorzi G, Marras C, Nardocci N, Franzini A, Chiapparini L, Maccagnano E, Angelini L, Caldiroli D, Broggi G (2005) Stimulation of the globus pallidus internus for childhood-onset dystonia. Mov Disord 20(9): 1194–1200

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Feed-forward control of post-stroke movement disorders by on-demand type stimulation of the thalamus and motor cortex

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Summary

Deep brain stimulation (DBS) of the thalamus (Vo/Vim) has become popular as a means of controlling involuntary movements, including post-stroke movement disorders. We have also found that post-stroke movement disorders and motor weakness can sometimes be controlled by motor cortex stimulation (MCS). In some forms of movement disorders, motor dysfunction becomes evident only when patients intend to move their body. We have developed an on-demand type stimulation system which triggers stimulation by detecting intrinsic signals of intention to move. Such a system represents feed-forward control (FFC) of involuntary movements. We report here our experience of DBS and MCS for controlling post-stroke movement disorders, and discuss the value of FFC. Excellent control of post-stroke movement disorders was achieved by conventional DBS and/or MCS in 20 of 28 patients with hemichoreoathetosis, hemiballism tremor, and motor weakness. FFC was tested in 6 patients who demonstrated excellent control of post-stroke postural tremor or motor weakness by conventional DBS or MCS. The on-demand stimulation provided satisfactory FFC in 4 of 4 patients with postural tremor and 2 of 2 patients with motor weakness, when the activity of muscles involved in posturing or intention to move was fed into the system. These findings justify further clinical studies on DBS and MCS in patients with post-stroke movement disorders. The on-demand type stimulation system may also be useful for overcoming various post-stroke movement disorders.

Keywords: Movement disorders; involuntary movement; stroke; deep brain stimulation; motor cortex; thalamus.

Introduction

During the last decade, deep brain stimulation (DBS) has become popular as a means of controlling involuntary movements. We have treated more than 400 patients with involuntary movements by DBS since 1989 [4–7, 10–12], including post-stroke movement disorders [6]. We have also found that involuntary movements can sometimes be attenuated in post-stroke patients undergoing motor cortex stimulation (MCS) for pain control [3, 5, 8]. This observation suggested that MCS may represent another useful option for controlling involuntary movements.

In some forms of movement disorders, involuntary movements are induced only when patients intend to move their body. We have developed an on-demand type stimulation system which triggers DBS or MCS by detecting intrinsic signals of intention to move. Such a system represents feed-forward control (FFC) of involuntary movements. In cases of postural tremor, for example, the tremor mechanism is activated by certain posturing. Signals related to posturing can therefore be used for FFC of the tremor. We report here our experience of DBS of the thalamus (Vo/Vim) and MCS for controlling post-stroke movement disorders, and discuss the value of FFC based on a preliminary study.

Materials and methods

A total of 28 patients with post-stroke movement disorders, including hemichoreoathetosis, hemiballism, tremor and motor weakness, underwent DBS and/or MCS. We employed DBS of the thalamus (Vo/Vim) for controlling the hemichoreoathetosis, hemiballism or tremor. In some patients with hemichoreoathetosis and/or tremor, the effects of MCS were tested separately before or after the subjects underwent Vo/Vim-DBS. MCS was also performed in 3 patients for the primary purpose of improving motor weakness. The stimulation intensity of the MCS was carefully restricted to below the threshold for muscle contraction. The stimulation frequency employed for the long-term use of MCS was limited to below 50 Hz.

We are currently employing the electromyographic (EMG) activity of appropriate muscles as an intrinsic signal to trigger DBS or MCS for the on-demand stimulation system. We first developed an on-demand type stimulation system, by connecting the system to the externalized leads during the test stimulation period before internalization. An external pulse generator is triggered by the EMG activity which is involved in tremor-inducing posture. We next developed an on-demand type stimulation system, which triggers an implanted pulse generator through a console programmer by detecting the appropriate combination of multiple EMG activities which best represents tremor-inducing posture. The implanted pulse generator is activated transcutaneously. We tested whether or not tremor is controlled satisfactorily in 4 patients with

Table 1. *Effects of conventional and on-demand type stimulation of the thalamus and motor cortex in patients with post-stroke movement disorders*

Movement disorders	n	Satisfactory control	
		Conventional stimulation	On-demand stimulation
DBS			
Hemiballism	3	3	0
Hemichoreoathetosis	8	5	0
Resting tremor	7	7	0
Postural tremor	7	4	4
MCS			
Motor weakness	3	2	2
Total	28	21 (75%)	6

post-stroke postural tremor by using these systems. In 2 patients with post-stroke motor weakness, MCS was triggered by EMG activity for intention to move, and the effect of stimulation on motor performance was evaluated subjectively. The above 6 patients comprised those who demonstrated excellent control of post-stroke postural tremor or motor weakness by conventional DBS or MCS.

Results

Excellent control of post-stroke involuntary movement was achieved by conventional DBS or MCS in 21 of the 28 patients (Table 1). In 2 patients, dual-lead DBS for stimulation of wide areas of the Vo/Vim was required to achieve satisfactory control. Some patients with post-stroke tremor preferred MCS to Vo/Vim-DBS. They underwent internalization of electrodes for MCS as well as DBS, and have so far used MCS to control their tremor for more than 8 years. The effects on tremor occurred at an intensity below the threshold for muscle contraction and at a relatively high frequency range. The inhibition of tremor was partial when the frequency was limited to below 50 Hz. The tremor under off-stimulation conditions disappeared in one patient after continuous MCS for more than 3 years. The on-demand stimulation system provided satisfactory FFC in 4 of the 4 patients with postural tremor and 2 of the 2 patients with motor weakness, when the EMG activities involved in posturing or intention to move were fed into the system.

Discussion

The present data confirm the benefits of MCS for controlling tremor in post-stroke patients. Post-stroke involuntary movements, especially those in thalamic syndrome, are sometimes associated with central pain. Vo/Vim-DBS could elicit opposite effects in these disorders. Involuntary movements can be attenuated, but the pain of the same patients may be exacerbated. MCS might represent the therapy of choice under such circumstances [2, 5].

We have found that patients who underwent MCS for pain control sometimes report subjective improvement of their motor performance, which had been impaired in association with motor weakness. It has also been reported that stimulation of the posterior limb of the internal capsule can attenuate motor deficits caused by cortical injury [1]. Such an effect is not attributable to objectively detectable muscle strength and appears to have resulted from an inhibition of the muscle rigidity.

DBS and MCS, if used with the on-demand type stimulation system, may also be useful for controlling other motor symptoms in post-stroke patients and for improving their overall motor performance. The present findings justify further clinical studies on DBS and MCS in patients with post-stroke movement disorders. The on-demand type stimulation system could be regarded as a first step towards the development of hybrid electric neural circuits to overcome various post-stroke movement disorders.

Conclusion

Future studies on cortical stimulation, including MCS and on-demand type stimulation systems, should clarify the clinical value of these techniques in controlling movement disorders. The present work was supported by a Grant-in-aid for Scientific Research (No. A12307029 and A15209047) from the Ministry of Science and Culture, Japan.

References

1. Fields H, Adams JE (1974) Pain after cortical injury relieved by electrical stimulation of the internal capsule. Brain 97: 169–178
2. Franzini A, Ferroli P, Dones I *et al* (2003) Chronic motor cortex stimulation for movement disorders. A promising perspective. Neurol Res 25: 123–126
3. Katayama Y, Fukaya C, Yamamoto T (1998) Post-stroke pain control by chronic motor cortex stimulation: neurological characteristics predicting favorable response. J neurosurg 89: 585–591
4. Katayama Y, Kasai M, Oshima H *et al* (2001) Subthalamic nucleus stimulation in Parkinson's disease. Benefits observed in levodopa-intolerant patients. J Neurosurg 95: 213–221
5. Katayama Y, Oshima H, Fukaya T *et al* (2001) Control of post-stroke movement disorders using chronic motor cortex stimulation. Acta Neurochir [Suppl] 79: 89–92
6. Katayama Y, Yamamoto T, Kobayashi K, Oshima H, Fukaya C (2003) Deep brain and motor cortex stimulation for post-stroke movement disorders and post-stroke pain. Acta Neurochir [Suppl] 87: 121–124

7. Tsubokawa T, Katayama Y, Yamamoto T (1995) Control of persistent hemiballismus by chronic thalamic stimulation. J Neurosurg 82: 501–505
8. Tsubokawa T, Katayama Y, Yamamoto T *et al* (1993) Chronic motor cortex stimulation in patients with thalamic pain. J Neurosurg 78: 393–401
9. Woolsey CN, Erickson T, Gilson WE (1979) Localization in somatic sensory and motor areas of human cerebral cortex as determined by direct recording of evoked potentials and electrical stimulation. J Neurosurg 51: 476–506
10. Yamamoto T, Katayama Y, Fukaya C *et al* (2001) New method of deep brain stimulation therapy using two electrodes implanted in parallel and side by side. J Neurosurg 95: 1075–1078
11. Yamamoto T, Katayama Y, Kobayashi K *et al* (2003) Dual-floor burr hole adjusted to burr-hole ring and cap for implantation of stimulation electrode. J Neurosurg 99: 783–784
12. Yamamoto T, Katayama Y, Kano T *et al* (2004) Deep brain stimulation for the treatment of parkinsonian, essential, and post-stroke tremor. A suitable stimulation method and changes in effective stimulation intensity. J Neurosurg 101: 201–209

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Pallidal high-frequency deep brain stimulation for camptocormia: an experience of three cases

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Summary

Introduction. The term ''camptocormia'' describes a forward-flexed posture. It is a condition characterized by severe frontal flexion of the trunk. Recently, camptocormia has been regarded as a form of abdominal segmental dystonia. Deep brain stimulation (DBS) is a promising therapeutic approach to various types of movement disorders. The authors report the neurological effects of DBS to the bilateral globus pallidum (GPi) in three cases of disabling camptocormia.

Methods. Of the 36 patients with dystonia, three had symptoms similar to that of camptocormia, and all of these patients underwent GPi-DBS. The site of DBS electrode placement was verified by magnetic resonance imaging (MRI). The Burke Fahn and Marsden dystonia rating scale (BFMDRS) was employed to evaluate the severity of dystonic symptoms preoperatively and postoperatively.

Results. Significant functional improvement following GPi-DBS was noted in the majority of dystonia cases. At a follow-up observation after more than six months, the overall improvement rate was $71.2 \pm 27.0\%$, in all dystonia cases who underwent the GPi-DBS. In contrast, the improvement rate of the three camptocormia cases was $92.2 \pm 5.3\%$. It was confirmed that the improvement rate for camptocormia was much higher than for other types of dystonia.

Conclusion. According to our experience, a patient with a forward-bent dystonic posture indicative of camptocormia is a good candidate for GPi-DBS. The findings of this study add further support to GPi-DBS as an effective treatment for dystonia, and provide the information on predictors of a good outcome.

Keywords: Camptocormia; GPi-DBS; dystonia.

Introduction

The term camptocormia is derived from two Greek words: kamptos (to bend, to crook) and kormos (trunk). A forced posture with a forward-bent trunk was termed camptocormia by the French neurologist Souques in 1915 [10]. It is a condition characterized by severe frontal flexion of the trunk, with passive dropping of both arms. Recently, camptocormia has been reported to occur in association with various other neurological conditions, including primary dystonia. The cause of this pathological condition remains unknown, and appropriate treatment has not been established.

Deep brain stimulation (DBS) has been regarded as a promising therapeutic approach for various types of movement disorders. The authors report the neurological effects of deep brain stimulation to the bilateral globus pallidum (GPi-DBS) in three cases of disabling camptocormia.

Methods

We analyzed follow-up data obtained from a consecutive series of 36 patients with dystonia who underwent functional stereotactic neurosurgical treatment. We have so far undertaken GPi-DBS in 36 patients with primary and secondary dystonias. The main inclusion criterion for DBS therapy for dystonia was that the patient was diagnosed as having dystonia refractory to any medications. The exclusion criteria included significant cognitive dysfunction, active psychiatric symptoms, and evidence of other central nervous system disease or other systemic medical disorders. Of the 36 patients, three patients had symptoms similar to that of camptocormia, and these three patients underwent GPi-DBS.

The methods of magnetic resonance imaging (MRI) and microelectrode-guided stereotaxy, and electrode implantation were performed in a similar way to previous reports [6, 7]. No sedation was employed during the surgery. The boundaries of the GPi were identified by MRI and confirmed by the recording of spontaneous neural activity using semimicroelectrodes (impedance: 0.2–0.5 Mohm). The trajectory of the semimicroelectrode was directed from the frontal burr hole at an angle of 45–60 degrees from the horizontal plane. A DBS electrode for chronic stimulation (Medtronic; Minneapolis, MN) was implanted into the trajectory, which had been confirmed to be appropriate.

The DBS electrode, which has 4 contact points numbered 0–3 sequentially from the most distal contact (0) to the most proximal contact (3),

was placed in such a way. The site of DBS electrode placement was verified by postoperative MRI. When DBS was found to be useful during the test stimulation period for a week, an implantable pulse generator (Soletora, Medtronic; Minneapolis, MN) was implanted into the subclavian region and connected to the DBS electrode. The stimulation parameters and contact points used for GPi-DBS were modified at each follow-up visit of the patients to our clinic on the basis of the results of neurological examination as well as patients' reports concerning the activity of daily life.

The BFMDRS (Burke Fahn and Marsden dystonia rating scale; maximum = 120) was employed to evaluate the severity of dystonic symptoms. In addition, an abdominal activity of selected muscle groups was studied by surface electromyography at rest and during the execution of simple tasks. These clinical studies were performed in each patient before surgery, at 6 months and every year after the surgery.

Case report

History

A right handed 46-year-old male who experienced a gradual onset and worsening of his forward bent dystonic posture was referred to our hospital. He was otherwise in good health. Neuroradiological examination including MRI showed normal findings. His abnormal forward bent dystonic posture and involuntary movements on his neck and abdomen were resistant to various medical treatments. His cognitive function was completely normal. He had no motor palsy and no obvious sensory deficit. His trunk was severely bent forward and continuous dystonic movements occurred mainly in the neck. When he walked, action-induced bending of the trunk markedly interfered with his gait. Electromyography before surgery demonstrated highly abnormal contractions of various muscles, particularly the rectus abdominis muscle. His score on the BMFDRS was 32 points before surgery.

Operation

The patient underwent MRI-guided stereotactic bilateral implantation of DBS electrodes targeted to the posteroventral segment of the GPi. DBS electrodes were implanted, placing contact point 0 at 4.5 mm below the midpoint between the anterior and posterior commissures, and 20 mm lateral to the midline. No surgical complications were encountered.

Postoperative course

A dramatic reduction in the abnormal muscular tone of the trunk and neck was noted immediately after the initiation of a high frequency stimulation to GPi (Fig. 1). Within several months after surgery, additional progressive improvements were noted. The maximum improvement was observed at 6 months after surgery. His score on the BMFDRS was 4 points at 6 months after surgery. No stimulation-related side effects were induced at stimulation intensity required for maximum effect. The maximum improvements have continued for more than 4 years to date.

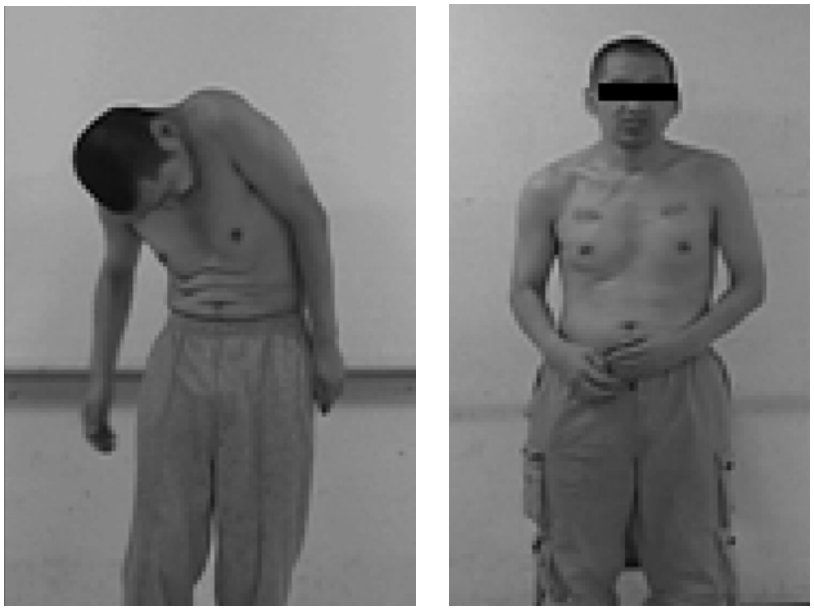

Fig. 1. A dramatic reduction in abnormal muscular tone of the abdomen was observed immediately after the initiation of high frequency stimulation to GPi

Table 1. *Changes in BMFDRS by GPi-DBS at the patients with camptocormia*

Case	Sex	Age	Onset age	Etiology	Score pre.	Score post.	Imp. rate
1	M	17y	13y	primary	50	0	100%
2	M	46y	45y	primary	32	4	91%
3	M	49y	44y	primary	48	32	83%
Mean improvement rate 92.2%							

Results

Significant functional improvements following GPi-DBS were noted in the majority of dystonia cases. There were no surgical complications or uncontrollable stimulation-related adverse effects. At a follow-up observation after more than 6 months, the overall improvement rate was $71.2 \pm 27.0\%$, as evaluated using the BFMDRS, in all dystonia cases that underwent the GPi-DBS. In contrast, the improvement rate of the three camptocormia cases was $92.2 \pm 5.3\%$ (Table 1). These findings suggest that the improvement rate for camptocormia, regarded as a form of abdominal segmental dystonia, was much higher than those of the other types of dystonia.

Discussion

The forced forward-bent trunk posture was termed camptocormia by French neurologist Souques in 1915 [10]. He presented four patients from the military hospital in France. Similar case reports are published as a psychogenic illness occurring among soldiers in World War I [4] and II [9].

Such pathological condition has been reported to occur in association with various other neurological conditions. In recent times, camptocormia has been regarded as a form of abdominal segmental dystonia. The following features were noted in patients suffering from camptocormia [5].

A curvature in the lumbar region only occurred in a sitting or standing position.

In the horizontal bodily position, this curvature entirely disappeared. In a prone position, even a hyperextension of the trunk could be achieved without pain by raising the legs passively.

The proper reflexes and sensitivity were normal, and pyramidal tract signs could not be found.

Radiographs of the spine were normal.

It is suggested that such movement disorder has been responsive to electrotherapy or to corticosteroids medications in some patients, whereas in others the disorder has been refractory to all attempted treatment strategies [5].

Chronic high-frequency DBS has been shown to improve functional status in a number of movement disorders of various causes. Especially, the effects of GPi-DBS on various forms of dystonia were reported previously by several authors [2, 3, 7, 11]. The improvement rates in score on the BMFDRS of various types of dystonia including primary or secondary as well as generalized or focal varieties reported in the literature have a wide range.

An excellent effect was reported especially in DYT1 [1]. Eltahawy HA and his colleagues [3] indicated that primary dystonia responds much better than secondary dystonia to pallidal procedure. Also, they mentioned that the presence of basal ganglia abnormalities demonstrated by preoperative MRI is an indicator of a poor response to pallidal intervention for dystonia. The use of GPi-DBS for treating dystonia is rapidly increasing and preliminary evidence suggests that dystonia linked to genetic mutation and other primary early-onset dystonias respond most dramatically to treatment by pallidal procedure [2, 11], whereas secondary dystonia tends to show a poor response [3].

The advantages of DBS include its relatively nondestructive nature, its adjustability and reversibility, and its capacity to be used bilaterally in a safe manner. Nandi and his colleagues [8] first reported the neurological effects of long-term bilateral palidal high-frequency DBS in a patient with disabling camptocormia. They obtained significant functional improvement following long-term pallidal stimulation, and some improvements were also noted in neurological scores.

Our report also shows the remarkable benefits of the application of GPi-DBS for camptocormia. From the results of our three camptocormia cases, such type of abdominal segmental dystonia is a good candidate for GPi-DBS. The findings of this study add further support to GPi-DBS as an effective treatment for dystonia, and provide the information on predictors of a good outcome.

Conclusion

According to our experience, a patient with a forward-bent dystonic posture indicative of camptocormia is a good candidate for GPi-DBS. This knowledge is important for providing an accurate prognostic information on the effect of GPi-DBS to patients and clinicians.

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References

1. Coubes P, Roubertie A, Vayssiere N, Hemm S, Echenne B (2000) Treatment of DYT1-generalised dystonia by stimulation of the internal globus pallidus. Lancet 355: 2220–2221
2. Coubes P, Cif L, El Fertit H, Hemm S, Vayssiere N, Serrat S, Picot MC, Tuffery S, Claustres M, Echenne B, Frerebeau P (2004) Electrical stimulation of the globus pallidus internus in patients with primary generalized dystonia: long-term results. J Neurosurg 101: 189–194
3. Eltahawy HA, Saint-Cyr J, Giladi N, Lang AE, Lozano AM (2004) Primary dystonia is more responsive than secondary dystonia to pallidal interventions: outcome after pallidotomy or pallidal deep brain stimulation. Neurosurgery 54: 613–619
4. Hurst AF (1918) The bent back of soldiers. Br Med J 2: 621–623
5. Karbowski K (1999) The old and the new camptocormia. Spine 24: 1494–1498
6. Katayama Y, Kasai M, Oshima H, Fukaya C, Yamamoto T, Ogawa K, Mizutani T (2001) Subthalamic nucleus stimulation for Parkinson disease: benefits observed in levodopa-intolerant patients. J Neurosurg 95: 213–221
7. Katayama Y, Fukaya C, Kobayashi K, Oshima H, Yamamoto T (2003) Chronic stimulation of the globus pallidus internus for control of primary generalized dystonia. Acta Neurochir [Suppl] 87: 125–128
8. Nandi D, Parkin S, Scott R, Winter JL, Joint C, Gregory R, Stein J, Aziz TZ (2002) Camptocormia treated with bilateral pallidal stimulation. J Neurosurg 97: 461–466
9. Sandler SA (1945) Camptocormia: a functional condition of the back in neurotic soldiers. War Med 8: 36–45
10. Souques A (1915) Contractures ou pseudo-contractures hystero-traumatiques. Rev Neurol 28: 430–431
11. Zorzi G, Marras C, Nardocci N, Franzini A, Chiapparini L, Maccagnano E, Angelini L, Caldiroli D, Broggi G (2005) Stimulation of the globus pallidus internus for childhood-onset dystonia. Mov Disord 20: 1194–1200

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Multimodal neurosurgical strategies for the management of dystonias

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Summary

Dystonia have many subtypes, and is classified as focal, segmental and generalized. As for focal dystonia, spasmodic torticollis (cervical dystonia) and writer's cramp are most common. Cervical dystonia is mainly treated effectively with selective peripheral denervation, and task specific focal dystonia of the hand (writer's cramp) is effectively alleviated by stereotactic ventro-oral thalamotomy. Generalized dystonia is dramatically improved with deep brain stimulation of the globus pallidus interna. Because the majority of dystonia is medically refractory and surgical treatment results in marked improvement, the authors strongly believe that dystonia should be regarded as a definite neurosurgical indication. Based on personal experience of nearly 200 cases of dystonia surgery, the authors describe a multimodal approach to various types of dystonias. Also we discuss possible relation between dystonias and psychiatric conditions, and future new indication of dystonia surgery.

Keywords: Dystonia; torticollis; writer's cramp; peripheral denervation; thalamotomy; deep brain stimulation.

Introduction

The term ''dystonia'' is used both as a name of disorder and a specific symptom. The range of symptoms is very wide and whether the underlying pathophysiology of various types of dystonia is uniform or not is not well known. In neurosurgical clinical practice, it is convenient to classify dystonias into pure cervical dystonia, task-specific focal hand dystonia, segmental and generalized dystonia. Because symptoms, signs, etiology, age, and so on differ greatly from patient to patient, we have to face various types of treatment modalities. We would like to introduce our consecutive experience of surgical management of these different types of dystonias.

Segmental and generalized dystonia

For segmental and generalized dystonia, the treatment of choice at present is bilateral globus pallidum interna (GPi) deep brain stimulation as in most other centers. When I started pallidal surgery for dystonia about six years ago, the electrical stimulation devices were not readily available. Therefore, I used to perform sequential bilateral pallidotomy, and then I moved unilateral pallidotomy (right side) and contralateral (left side) pallidal DBS. However, since 3 years ago, it has become our routine to implant bilateral pallidal DBS for generalized and segmental dystonia. Our method does not differ from those of other centers; MRI/CT fusion stereotaxi. Initially we used intravenous propofol sedation to control intraoperatively unnecessary movements and found that the dystonia symptoms worsened in some patients with light propofol anesthesia [2, 10]. We then found several reports that dystonia is induced by propofol anesthesia, and since then we have been using intravenous dexmedetomidine hydrochloride that is generally used for sedation in the intensive care unit.

In Japan, DYT-1 dystonia is not common because of genetic and racial factors, and the majority of our cases are adult onset idiopathic dystonia without family history. Some of them had a history of psychiatric problems treated with antipsychotic medication, and the symptoms may be classified as tardive dyskinesia, but response to pallidal DBS is generally the same as those without such a psychiatric history. We also experienced some cases of dystonias due to hereditary metabolic disorders such as Lesch-Nyhan syndrome and Hallervorden-Spatz syndrome with favorable results [9].

Although it is evident that the optimal target for dystonia lies in the GPi, it is not known whether the traditional GPi target used for control of Parkinson's disease (PD) is best for dystonia. Also many of the patients with dystonia tend to be obsessive or in an excessive anxiety state, which indicates that the background pathophysiology of dystonia also involves limbic pallidum that is

anterior to the GPi target for control of motor symptoms. To explore a better stimulation area and to find any psychological changes with DBS in the more anterior pallidum, we usually implant two DBS electrodes on one side, resulting in four electrodes implanted in the brain. The posterior electrode is in the traditional GPi for PD, and the anterior electrode is placed 3 mm anteriorly. We generally externalized the lead and perform trial stimulation over three weeks to find the best motor effect and to see psychological changes. The details of this investigation will be published in the near future. After GPi stimulation, involuntary dystonic movements improve within hours, but abnormal fixed postures of the trunk, neck, and extremities tend to respond much later.

The indication or the role of GPi DBS for cervical dystonias (CD) has not yet been established [4]. However, based on our experience of 132 CD patients treated with selective peripheral denervation, we strongly believe that GPi DBS is definitely indicated in the complex type of CD. Complex type of CD is characterized by irregular involuntary head and neck movements and diffuse bilateral involvement of the neck muscles.

Cervical dystonia

Neurosurgical treatment of CD has a long history. In the beginning, the sternocleidomastoid muscle (SCM) and the accessory nerve were the target of surgical intervention. Then the importance of the posterior neck muscles, mainly the splenius muscle (SPL), was recognized. In order to denervate the accessory and cervical spinal nerves innervating to SCM and SPL, intradural rhizotomy was started, with some benefit. But inadequate denervation of SPL and complications due to denervation of normal muscles, turned out to be a problem. Some performed spinal cord stimulation to mimic sensory trick phenomenon. Bertrand [1] started and established selective peripheral denervation in which selective and complete denervation of the posterior neck muscles was accomplished by denervating the extradural dorsal rami of C1–C6 spinal nerves. This is now regarded as the safest and most effective neurosurgical treatment for the majority of CD. We modified this procedure to further minimize the side effects [6]. It is important to remember that the levator scapulae muscle is also involved in some CD patients resulting in lateral tilt of the head and elevation of the shoulder. In such cases, selective denervation of the levator scapulae muscle is safely performed [8]. Although peripheral denervation is a symptomatic treatment, many of the patients can enjoy symptom free life afterwards as if background pathophysiology was completely cured. As mentioned previously, in some complex type of CD and CD with extracervical symptoms, our preference is GPi DBS.

Task-specific focal hand dystonia

The most common type of task-specific focal hand dystonia is writer's cramp and musician's cramp. Such condition is very miserable, especially when the symptom is related with the patient's profession. As there have been some case reports on thalamotomy for writer's cramp, we started ventrooral thalamotomy for task-specific focal hand dystonia about five years ago [7]. This was because botulinum toxin injection is not approved in Japan for symptoms other than neck and face dystonias. The ventrooral nucleus of the thalamus receives inputs from GPi and forms part of the thalamocortical-basal ganglia loop. Task-specific focal hand dystonia is regarded as the result of oscillation of this cerebral circuit, and making a small lesion in this loop to de-sensitize the loop is the theoretical background of this treatment. So far we have treated 22 patients with writer's cramp and four with musician's cramp. Immediately after the operation, the effect is generally dramatic, but the problem is that recurrence rate is about 15% of patients. Such recurrence seems to be due to inadequate lesioning, because true lesioning and temporary thermal effect are difficult to distinguish during surgery. However, it is evident from our experience that we can cure writer's cramp and musician's cramp with ventrooral thalamotomy with minimal risk. There have been no permanent complications, though transient (2–3 weeks) mild limb weakness and dysarthria were seen in a few patients. One may argue why we do not perform DBS instead of lesioning. This is of course debatable, but the main reason is that DBS merely leads to suppression of the symptom, but thalamotomy can result in permanent cure. DBS itself has disadvantages in terms of hardware complications and psychological burden on the patients; they are living with a device and the disease itself is not cured. Patients with focal hand dystonia are generally young (32 years old on average in our series), and the risk of thalamotomy is supposed to be lower than in aged population as in PD patients. Recovery from complications, if any, is considered faster and more complete.

Recently we found task-specific focal ''foot'' dystonias among semi-professional speed skaters. The symptom appears only when they skate, and the foot moves at the ankle joint laterally like valgus. This condition is

well-known among Olympic level skaters in Japan and they call it Burabura (floppy) disease in slang.

Issue on dystonia and psychiatric conditions

It is well known that patients with dystonia tend to have a particular psychological or mental character. Patients with CD are often depressive, aggressive, but occasionally obedient. Focal hand dystonia patients are often obsessive, and perfect and impeccable pursuit. Those with DYT-1 dystonia are almost always bright, clever, intelligent. Patients with dystonias may develop psychiatric problems even after treatment of the physical symptoms, and it is also well known that psychiatric disorders are sometimes followed by movement disorders called tardive dyskinesia and dystonia. Thus movement disorders, especially dystonia, seem to be closely related with psychiatric or mental conditions. Dystonia is regarded as an expression of dysfunction of the thalamo-cortical-basal ganglia motor loop, but there are many other loop circuits in the brain and dysfunction of some of these loops are responsible for psychiatric disorders such as depression and obsessive disorders. The motor and mental functions of the brain are basically the output (efferent) system. Therefore, as there are many motor disorders as shown in Table 1, there must be corresponding psychiatric disorders such as mental tremor, mental dystonia, mental spasticity, mental dyskinesia, and so on. We assume these conditions are generally and traditionally called psychiatric disorders such as depression, obsession, compulsion, anxiety, and so on. Therefore, it is reasonable that surgical treatment of intractable psychiatric problems now attracts many functional neurosurgeons in a similar way as movement disorder surgery.

Table 1

Motor symptoms	Possible mental symptoms	Traditional mental and psychiatric symptoms
Tremor	mental tremor	depression
Ataxia	mental ataxia	obsession
Dystonia	mental dystonia	compulsion
Chorea	mental chorea	anxiety
Ballism	mental ballism	mania
Dysmetry	mental dysmetry	schizophrenia
Spasticity	mental spasticity	personality disorder
Apraxia	mental apraxia	mental retardation
Palsy	mental palsy	etc
etc	etc	

New possible indication of dystonia surgery

There are some mysterious and unsolved movement or posture problems that are often regarded as due to hysteria or mental instability. One is stuttering and another is idiopathic scoliosis. There is a report that scoliosis may be linked to the occurrence of cervical dystonia, perhaps as a forme fruste of a genetic dystonic predisposition [3]. Stuttering is also suggested as a type of dystonia [5]. We may in future become able to solve such difficult but important problems based on the knowledge of neurosurgical treatment of dystonia.

References

1. Bertrand CM (1993) Selective peripheral denervation for spasmodic torticollis: surgical technique, results, and observations in 260 cases. Surg Neurol 40(2): 96–103
2. Bragonier R, Bartle D, Langton-Hewer S (2000) Acute dystonia in a 14-yr-old following propofol and fentanyl anaesthesia. Br J Anaesth 84(6): 828–829
3. Duane DD (1998) Frequency of scoliosis in cervical dystonia patients and their relatives. Mov Disord 13(2): 99
4. Kiss ZH, Doig K, Eliasziw M, Ranawaya R, Suchowersky O (2004) The Canadian multicenter trial of pallidal deep brain stimulation for cervical dystonia: preliminary results in three patients. Neurosurg Focus 17(1): E5
5. Kiziltan G *et al* (1996) Stuttering may be a type of action dystonia. Mov Disord 11: 278–282
6. Taira T, Kobayashi H, Takahashi K, Hori T (2002) A new denervation procedure for idiopathic cervical dystonia. J Neurosurgery (Spine) 97: 201–206
7. Taira T, Hori T (2003) Stereotactic ventrooralis thalamotomy for task-specific focal hand dystonia (writer's cramp). Stereotact Funct Neurosurg 80: 88–91
8. Taira T, Kobayashi T, Takahashi K, Hori T (2003) Selective peripheral denervation of the levator scapulae muscle for laterocollic cervical dystonia. J Clin Neurosci 10: 449–452
9. Taira T, Kobayashi T, Hori T (2003) Disappearance of self mutilating behavior in a patient with Lesch-Nyhan syndrome after bilateral chronic stimulation of the globus pallidus internus. J Neurosurg 98: 414–416
10. Zabani I, Vaghadia H (1996) Refractory dystonia during propofol anaesthesia in a patient with torticollis-dystonia disorder. Can J Anaesth 43(10): 1062–1064

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Detection of boundaries of subthalamic nucleus by multiple-cell spike density analysis in deep brain stimulation for Parkinson's disease

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Summary

When microelectrode recording of single cell activity is employed for targeting the subthalamic nucleus (STN), multiple sampling of single cells is needed to determine whether the electrode has passed through the ventral boundaries of the STN. In contrast, stepwise recording of multiple cell activities by a semimicroelectrode reveals robust changes in such activities at the dorsal and ventral boundaries. We attempted to quantify changes in multiple cell activities by computing multiple-cell spike density (MSD). We analyzed MSD in 60 sides of 30 patients with Parkinson's disease. Neural noise level was defined as the lowest cut-off level at which neural noise is separated from larger amplitude spikes. MSD was analyzed at cut-off levels ranging from 1.2 to 2.0-fold the neural noise level in the white matter in each trajectory. Both the dorsal and ventral boundaries were clearly identified by an increase and a decrease ($p < 0.0001$) in MSD, respectively, in all the 60 sides. The cut-off level of 1.2-fold showed the clearest change in MSD between the STN and the pars reticulata of substantia nigra. MSD analysis by semimicroelectrode recording represents the most practical means of identifying the boundaries of STN.

Keywords: Parkinson's disease; deep brain stimulation; subthalamic nucleus; substantia nigra, microelectrode; semimicroelectrode.

Introduction

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) affords great benefits to the daily activities in patients with advanced Parkinson's disease (PD) [4, 5, 7]. Most of recent reports have placed emphasis on microelectrode recording of single cell activity for refining the anatomical targeting of the STN during surgery [1, 2, 8–10]. The ventral boundary of the STN is, however, sometimes unclear [9]. Because a microelectrode detects only electrical events arising from a small area, multiple sampling of single cell activity is needed by changing the location of the electrode tip to determine whether the electrode has passed through the ventral boundary of the STN and entered the pars reticulata of substantia nigra (SNr).

We have been employing semimicroelectrode recording [4, 6, 11, 12] for many years to refine anatomical targeting. A semimicroelectrode could detect electrical events arising from a relatively wide area. This method results in stable recordings of spikes and neural noise generated by multiple cells at any locations of the electrode tip.

Semimicroelectrode recording of multiple cell activities reveals robust changes in such activities at the dorsal and ventral boundaries, and therefore appears to be more practical and time-saving. Little has yet been reported, however, regarding the standardization of such a technique. In this study, we attempted to quantify changes in multiple cell activities by computing multiple-cell spike density (MSD).

Materials and methods

We analyzed data obtained from semimicroelectrode recording in 30 patients of Parkinson's disease, who underwent single stage surgery for bilateral STN-DBS. These patients were diagnosed as having idiopathic PD; they demonstrated past evidence of a good response to levodopa, but showed severe motor symptoms despite medications at tolerable doses and appropriate schedule. The patients' Hoehn and Yahr stage with medication was within the range from Stage III to V during the off-period, and from Stage II to IV during the on-period. The patients and their families gave informed consent for all procedures.

Indirect magnetic resonance (MR) imaging-based anatomic targeting was used. Employing Leksell SurgiPlan® (Elekta Instruments AB, Stockholm, Sweden), the MR images were reconstructed, and both the anterior commissure (AC) and the posterior commissure (PC) were identified. AtlasSpace® (Elekta Instruments AB, Stockholm, Sweden) could superimpose the digitized version of the Schaltenbrand-Wahren atlas on patient's MR images. The tentative target was defined as the posterolateral STN. A burr hole was made 30–35 mm anterior to the coronal suture and 20–25 mm lateral to the midline [11–13]. The STN

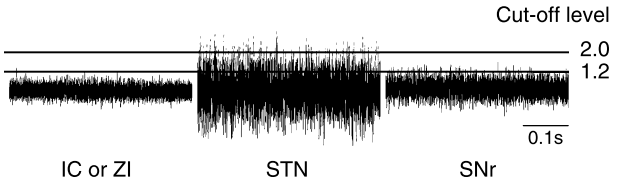

Fig. 1. Cut-off levels for analyzing the MSD were set in the ranging from 1.2, 1.4, 1.6, 1.8, and 2.0-fold the neural noise level in IC or ZI. This is because as the electrode enters the STN, neural noise level increased more than 2.0-fold of the level in the IC or ZI, MSD within the STN reflects both spikes and sharp compound waves, although spikes are predominantly represented at higher cut-off levels. *IC* Internal capsule; *ZI* zona incerta; *STN* subthalamic nucleus; *SNr* pars reticulata of substantia nigra; *MSD* multiple-cell spike density

was approached from the burr hole at an angle of 40–50 degrees to the horizontal plane parallel to the AC-PC line and 0–12.5 degrees to the sagittal plane.

Neural activities were recorded with a pencil-shaped bipolar concentric type semimicroelectrode (Unique Medical Co., Tokyo, Japan). The diameter of exposed tip was approximately 0.1 mm, and the interpolar distance was 0.5 mm with an electrical resistance of 0.2 Mohm at 1000 Hz. The catheter needle was first inserted and advanced to a point 10 mm above the tentative target, and the tip of the semimicroelectrode was advanced in consecutive 0.25 mm increments from a depth of 10 mm above the tentative target by employing a hydraulic microdrive (Narishige Co., Tokyo, Japan). The recording first yielded the anterior thalamic nucleus or the internal capsule (IC), and this was always followed by the zona incerta (ZI) and Forel H fields before entering the STN. In addition, the semimicroelectrode was further advanced 3 mm from the tentative target to confirm the border between the STN and the SNr. Signals were amplified, filtered (300 Hz–10 kHz), displayed on an oscilloscope, played on an audio monitor, and stored in a data recorder.

Electrical events recorded by the semimicroelectrode included spikes with variable amplitudes arising from multiple cells as well as neural noise, i.e., the fluctuation in field potentials generated by various neural elements. Large amplitude spikes could be separated from neural noise by setting an appropriate cut-off level of amplitude. However, it was not always possible to separate small or medium-sized spikes from sharp compound waves, which are contained in the neural noise. We therefore computed the density of spikes and sharp compound waves together, as MSD, counting their occurrence at various cut-off levels.

In the final tracking by semimicroelectrode recording, we determined neural noise level in the IC or ZI. Neural noise level was defined as the lowest cut-off level at which neural noise is separated from larger amplitude spikes. MSD at a given recording site was analyzed at cut-off levels ranging from 1.2 to 2.0-fold the neural noise level in the IC or ZI (Fig. 1). Because MSD within the STN reflects both spikes and sharp compound waves, differences in MSD at all 0.25 mm increments of the electrode were compared for the detection of the dorsal and ventral boundaries of the STN. Also, MSD recorded at every 0.25 mm increment was averaged in each structure, and used for the comparison between the IC or ZI, the STN, and the SNr.

The data are expressed as the mean ± standard deviation. For statistical analysis, Mann-Whitney's U test was used for comparison of MSD. If the probability value was less than 0.05, the difference was considered to be significant. This study was approved by the institutional committee for clinical research on humans.

Results

When the electrode enters the STN, neural noise level raised more than 2.0-fold the level in the IC or ZI,

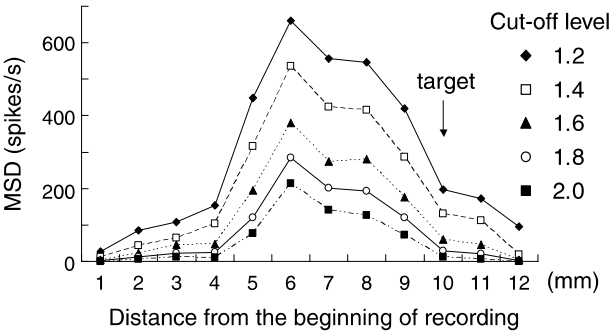

Fig. 2. Representative example of changes in the MSD at STN. Cut-off level was varied from 1.2 to 2.0-fold the neural noise level at the IC. The MSD increased at 5 mm from the point where recording was initiated, and decreased at the tentative target point (10 mm)

and spikes are predominantly observed at higher cut-off levels. MSD clearly increased when the electrode crossed the dorsal boundary of the STN, and decreased when the electrode passed through the ventral boundary of the STN and entered the SNr. MSD within the STN was larger than MSD in IC or ZI and MSD in the SNr at any cut-off levels ranging from 1.2 to 2.0-fold (Fig. 2). The cut-off level of 1.2-fold showed the largest increase in MSD in the STN (584 ± 195 spikes/s), which was markedly higher than MSD in IC or ZI (16 ± 9 spikes/s; $p < 0.0001$, $n = 60$) and SNr (94.1 ± 80.8 spikes/s; $p < 0.0001$, $n = 60$; Fig. 3) at this cut-off level. The dorsal and ventral boundaries of the STN were clearly identified by the increase and decrease in MSD, respectively, in all the 60 sides.

Immediately after the stereotactic operation was completed, we performed MR imaging again, and the location of contact points of the DBS electrode was confirmed. The mean distance of the DBS electrode from the midline in

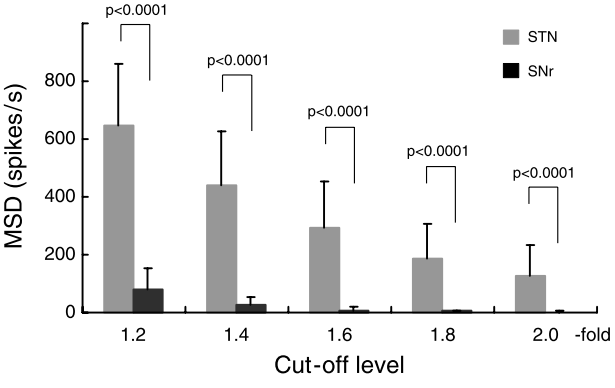

Fig. 3. Graphs demonstrate the comparison of MSD between STN and SNr at each cut-off level. The cut-off level of 1.2-fold showed the most obvious changes. MSD recorded in STN are significantly higher than MSD in SNr ($p < 0.0001$). *MSD* Multiple-cell spike density; *STN* subthalamic nucleus; *SNr* pars reticulata of substantia nigra

the present series of patients is 11.3 mm, which is the same as the distance reported previously (11–12 mm) [2, 9].

Discussion

In this study, we demonstrated that MSD clearly increased when the electrode entered the STN. In the typical recording within the STN reported by Starr *et al.* [9], large amplitude spikes from multiple cells and elevated neural noise level were observed. The increase in MSD at the dorsal boundary of the STN is consistent with these findings.

The discharge rate of STN cells is approximately half of the discharge rate of SNr cells if analyzed as single cell activity by microelectrode recording. Hutchison *et al.* [3] reported that, although STN cells show discharge with an irregular pattern at varying rate ranging from 25 to 45 Hz (37 ± 17 Hz), SNr cells exhibit a discharge with more regular pattern at a much faster rate (71 ± 23 Hz). Their results indicate that background multiple cell activities are higher in the SNr than in the STN. Starr *et al.* [9] also reported that cells in the SNr show a discharge at faster rate (86 ± 16 Hz) as compared to cells in the STN (34 ± 14 Hz).

In contrast to these previous reports on microelectrode recording, MSD was always higher in the STN than in the SNr in this study. Background multiple cell activities may vary in microelectrode recording depending on the location of the electrode tip. The discrepancy in spike density (discharge rate) between studies employing microelectrodes and semimicroelectrodes appears to reflect the difference in the capability of detecting information regarding cell density in addition to the discharge rate of cells in average.

In this study, the lowest cut-off level of 1.2-fold showed the largest changes. This is obviously because MSD at such a cut-off level includes fluctuation in field potential which becomes larger in amplitudes within the STN. Since an increase in amplitude in field potential may also reflect increases in multiple cell activities as well as the cell density, the significance of MSD analysis may not differ at any cut-off level for determining the boundaries of the STN.

In conclusion, this study demonstrated that MSD analysis by semimicroelectrode recording represents the most practical means of identifying the boundaries of STN.

Acknowledgement

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References

1. Cuny E, Guehl D, Burbaud P, Gross C, Dousset V, Rougier A (2002) Lack of agreement between direct magnetic resonance imaging and statistical determination of a subthalamic target: the role of electrophysiological guidance. J Neurosurg 97: 591–597
2. Hamid NA, Mitchell RD, Mocroft P, Westby GW, Milner J, Pall H (2005) Targeting the subthalamic nucleus for deep brain stimulation: technical approach and fusion of pre- and postoperative MR images to define accuracy of lead placement. J Neurol Neurosurg Psychiatry 76: 409–414
3. Hutchison WD, Allan RJ, Opitz H, Levy R, Dostrovsky JO, Lang AE, Lozano AM (1998) Neurophysiological identification of the subthalamic nucleus in surgery for Parkinson's disease. Ann Neurol 44: 622–628
4. Katayama Y, Kasai M, Oshima H, Fukaya C, Yamamoto T, Ogawa K, Mizutani T (2001) Subthalamic nucleus stimulation for Parkinson disease: benefits observed in levodopa-intolerant patients. J Neurosurg 95: 213–221
5. Krack P, Batir A, Van Blercom N, Chabardes S, Fraix V, Ardouin C, Koudsie A, Limousin PD, Benazzouz A, LeBas JF, Benabid AL, Pollak P (2003) Five-year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson's disease. N Engl J Med 349: 1925–1934
6. Lanotte MM, Rizzone M, Bergamasco B, Faccani G, Melcarne A, Lopiano L (2002) Deep brain stimulation of the subthalamic nucleus: anatomical, neurophysiological, and outcome correlations with the effects of stimulation. J Neurol Neurosurg Psychiatry 72: 53–58
7. Limousin P, Krack P, Pollak P, Benazzouz A, Ardouin C, Hoffmann D, Benabid AL (1998) Electrical stimulation of the subthalamic nucleus in advanced Parkinson's disease. N Engl J Med 339: 1105–1111
8. Priori A, Egidi M, Pesenti A, Rohr M, Rampini P, Locatelli M, Tamma F, Caputo E, Chiesa V, Barbieri S (2003) Do intraoperative microrecordings improve subthalamic nucleus targeting in stereotactic neurosurgery for Parkinson's disease? J Neurosurg Sci 47: 56–60
9. Starr PA, Christine CW, Theodosopoulos PV, Lindsey N, Byrd D, Mosley A, Marks WJ Jr (2002) Implantation of deep brain stimulators into the subthalamic nucleus: technical approach and magnetic resonance imaging-verified lead locations. J Neurosurg 97: 370–387
10. Starr PA, Vitek JL, DeLong M, Bakay RA (1999) Magnetic resonance image-based stereotactic localization on the globus pallidus and subthalamic nucleus. Neurosurgery 44: 303–313
11. Yamamoto T, Katayama Y, Fukaya C, Oshima H, Kasai M, Kobayashi K (2001) New method of deep brain stimulation therapy with two electrodes implanted in parallel and side by side. J Neurosurg 95: 1075–1078
12. Yamamoto T, Katayama Y, Kano T, Kobayashi K, Oshima H, Fukaya C (2004) Deep brain stimulation for the treatment of Parkinsonian, essential, and poststroke tremor: a suitable stimulation method and changes in effective stimulation intensity. J Neurosurg 101: 201–209
13. Yamamoto T, Katayama Y, Kobayashi K, Oshima H, Fukaya C (2003) Dual-floor burr hole adjusted to burr-hole ring and cap for implantation of stimulation electrodes. J Neurosurg 99: 783–784

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Microelectrode recording: lead point in STN-DBS surgery

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Summary

Background. Microelectrode recording is an integral part of many surgical procedures for movement disorders. We evaluate the Lead point compared to the NeuroTrek system. We used NeuroTrek in 18 Parkinsonian patients, Lead point-4 in 12 patients, during STN-DBS surgery. We compared MR-Stir image with Microelectrode recording.

Method. The MicroGuide system with its integrated screen display provides the user with all the information needed during the surgery on its screen. Microelectrode recordings showed characteristic neuronal discharges on a long trajectory (5–6 mm), intraoperative stimulation induces dramatic improvement of Parkinsonian motor symptoms.

Findings. Microrecording data of the Leadpoint showed high background activity, and firing rate of 14–50 Hz. The discharge pattern is typically chaotic, with frequent irregular bursts and pauses.

Discussion. The microelectrode recording of the neuroTrek and Leadpoint-4 showed unique results of the typical STN spike. The DBS effect is maximized associated by MER mapping.

Keywords: Parkinsonian; microelectrode recording; STN-DBS; intraoperative stimulation.

Introduction

Microelectrode recording is an integral part of many surgical procedures for movement disorder. In the past, clinicians and researchers had to create their own microrecording systems from separately purchased components. This practice resulted in a variety of setups, and many clinical centers are still using these ''home made'' systems [16]. Most of the commercially available microrecording devices are Neurotrek (MicroGuide), Lead point 2/Lead point 4, NeuroMap, Guideline system 3000A, Iso-X cell 3+/Iso Pulsar/micro Targeting, etc [16]. We used the Lead point-4 and Neurotrek (MicroGuide) in STN-DBS surgery of the Parkinsonism. I analysed microelectrode findings in subthalamic nucleus and substania nigra.

Materials and methods

Eighteen Parkinsonism patients for treatment with neuroTrek were enrolled between September, 2001 and August, 2002. in Oregon Health & Sciences University, Portland, OR, USA, and twelve Parkinsonism patients for Lead point-2/4 treatment between November, 2004 and March, 2005 in Busan Paik Hospital, Busan, Korea.

Bilateral electrodes were implanted stereotactically under local anesthesia in a single operation. Magnetic resonance imaging (T1, fast spin echo inversion recovery, Stir) was used to determine initial targets.

Although there is considerable variation, an approximate target for the central region of the STN nucleus is usually at about 12 mm lateral to the midline, 2–4 mm posterior to the mid-commissural point and 3 mm below the AC-PC line, with Stealth station (Medtronic, Sofamor, Mineapolis, USA) or Gamma-Plan (Elekta, Atlanta, USA). In our procedure, microelectrode recording tracks starts 10 mm above target in the STN. Depending on the 55–60° angle in the sagittal plane, recording usually starts in the thalamic reticular nucleus or in the anterior thalamus Voa, Vop.

In this region there are cells with spontaneous burst discharge [13, 14]. The entry into the subthalamic nucleus is apparent when high amplitude spikes with firing rates of 25–45 Hz are found [8].

Tremor cells have also been identified in the human subthalamic nucleus. Since subthalalmic nucleus-like cells may be found in the adjacent, superiorly located zona incerta, the dorsal border of the subthalamic nucleus should be defined by a continuous, cell-dense region, populated by neurons showing movement-related activity [8]. Typically, subthalamic spike is chaotic with frequent irregular bursts and pauses [8]. Below the STN, the substantia nigra, is located whose characteristic features are a high (60–90 Hz) and regular firing rate, but there may be another group with lower rates around 30 Hz [3–5, 7]. The ideal target is defined as one showing clinical benefit and minimal adverse effects after stimulation through the DBS electrode. The position of the Medtronic 3387 quadripolar DBS electrode is chosen so that the 4 electrodes contracts span the 5–6 mm of the subthalamic nucleus [8]. This means that one contact is usually placed in the substantia nigra, two contacts within the subthalamic nucleus, and the superior contact in the zona incerta [8].

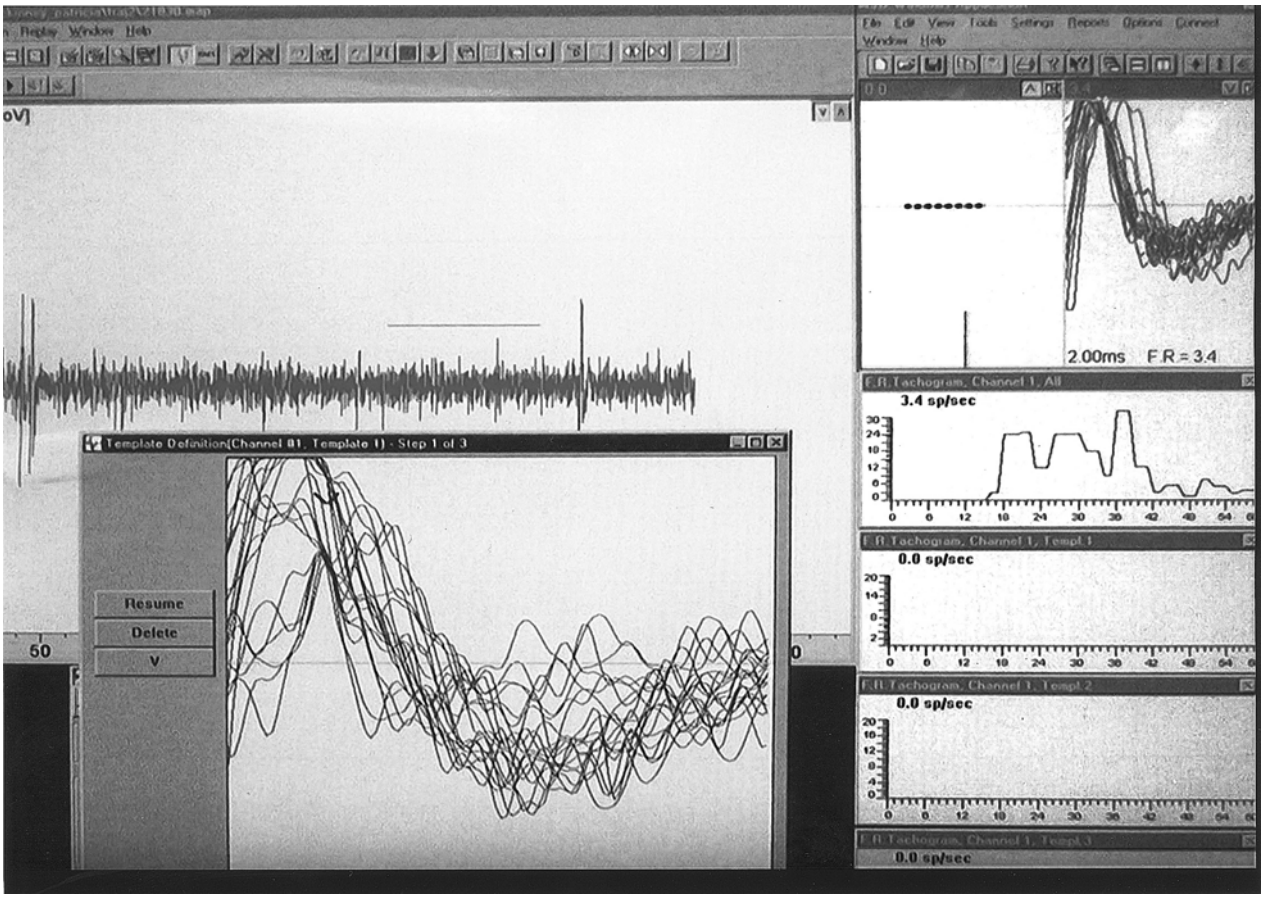

Fig. 1. Subthalamic nucleus microelectrode finding in Neurotrek

Table 1. *Characteristic mean firing rates of subthalamic regions encountered during microelectrode recordings*

	STN mean discharge rate (Hz)	STN cells recorded	SNr mean discharge rate (Hz)	SNr cells
Theodosopoulos *et al.* [17]	34	102	86	6
Hutchison *et al.* [8]	37	248	71	56
Pidoux *et al.* [19]	39	45	50–60	
Magnin *et al.* [10]	41	24		
Lozano *et al.* [7]	46	213		
Rodriguez *et al.* [15]	33	200	71	27
Magarinos-Ascone *et al.* [9]	59–69	190		
Kim *et al.* [our study]	14–52			

Gielen FLH [5], described 5 channels tracing of the Lead-point Microelectrode recording and the spikes of the center, lateral, posterior spikes showed excellent view (Figs. 2, 3). Usually, I used 3–5 channels for microelectrode recording. In our study, the mean depth of the subthalamic nucleus was 6–7 mm and our microelectrode recording of the Lead point-4 showed excellent view in center, posterior, lateral, anterior order (Fig. 4).

The follow-up is between 6 and 48 months, with a median 28 months. There were no permanent complications from the procedure. Postoperatively, thin section brain CT was checked and DBS location confirmed.

Results

In our study, the spikes of the subthalamic nucleus showed high-amplitude spikes with firing rates of 14–52 Hz (Fig .1). This is similar to other studies (Table 1).

Discussion

Bressand *et al.* [1] showed that there can be remarkable improvement of motor symptoms in Parkinsonism with bilateral deep brain stimulation of the subthalamic nucleus.

The most compact of all commercially available microrecording systems is developed and commonly used machine is Microguide. Lead point (Medtronic, Skovlundae, Denmark, and Shoreview, MN) is designed for single and multiple microelectrode recording capable of single-cell isolation and FDA cleared [16].

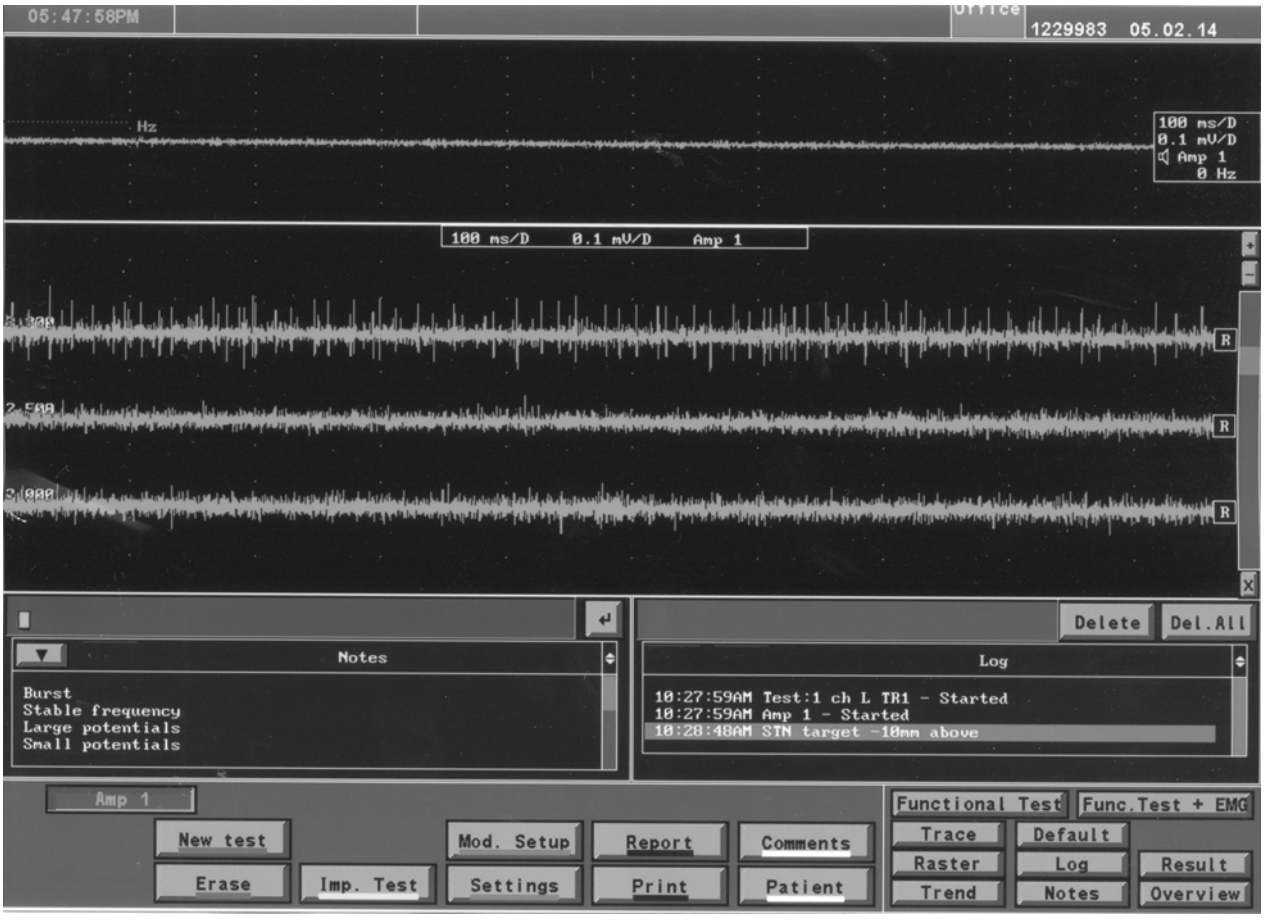

Fig. 2. Subthalamic nucleus microelectrode finding in Lead point 2

The system is delivered in two versions: Lead point 2 accommodates two microelectrodes, and Lead point 4 may simultaneously record from four electrodes, with the fifth electrode being switchable.

Lead point 4.0 is available in Europe now, and will soon be available to U.S. users [16]. For microelectrode navigation Lead point uses the microTargeting drive by Frederick Haer & Co. From a nonacademic user point of view, the system is a very good choice because it is compact, easy to use, has good quality of recording/amplification, and is less expensive than its competitors. Another advantage of Lead point is its potential integration with frameless navigation systems that may effectively eliminate the need for multiple instrumentation racks in an already crowded operating room [16].

Anatomic studies have shown somatotopically organized projections to the subthalamic nucleus from various parts of the frontal cortex. An autoradiographic tracer study in macaque monkeys showed motor cortex projections representing the face, arm, and leg arranged lateral to medial within the dorsolateral part of the nucleus [11]. More recently, a study of anterograde tracer injection after intracortical microstimulation mapping in macaque monkeys showed that the facial, forelimb, and hindlimb primary motor cortex projected to the lateral subthalamic nucleus in a lateral to medial arrangement [12]. Similar parts of the supplementary motor area projected in an inverse order into a more medial part of the nucleus [12].

Electrophysiological studies in the normal monkey reveal a predominance of cells responsive to somatosensory examination in the dorsolateral part of the STN [3, 18]. Cells representing the hindlimb are located centrally within this part of the nucleus, whereas forelimb cells are primarily encountered laterally and at the rostral and caudal poles. In a study of Parkinsonian humans undergoing STN surgery, leg-related cells were medial, arm-related cells were lateral, and orofacial cells were located in an intermediate zone [15].

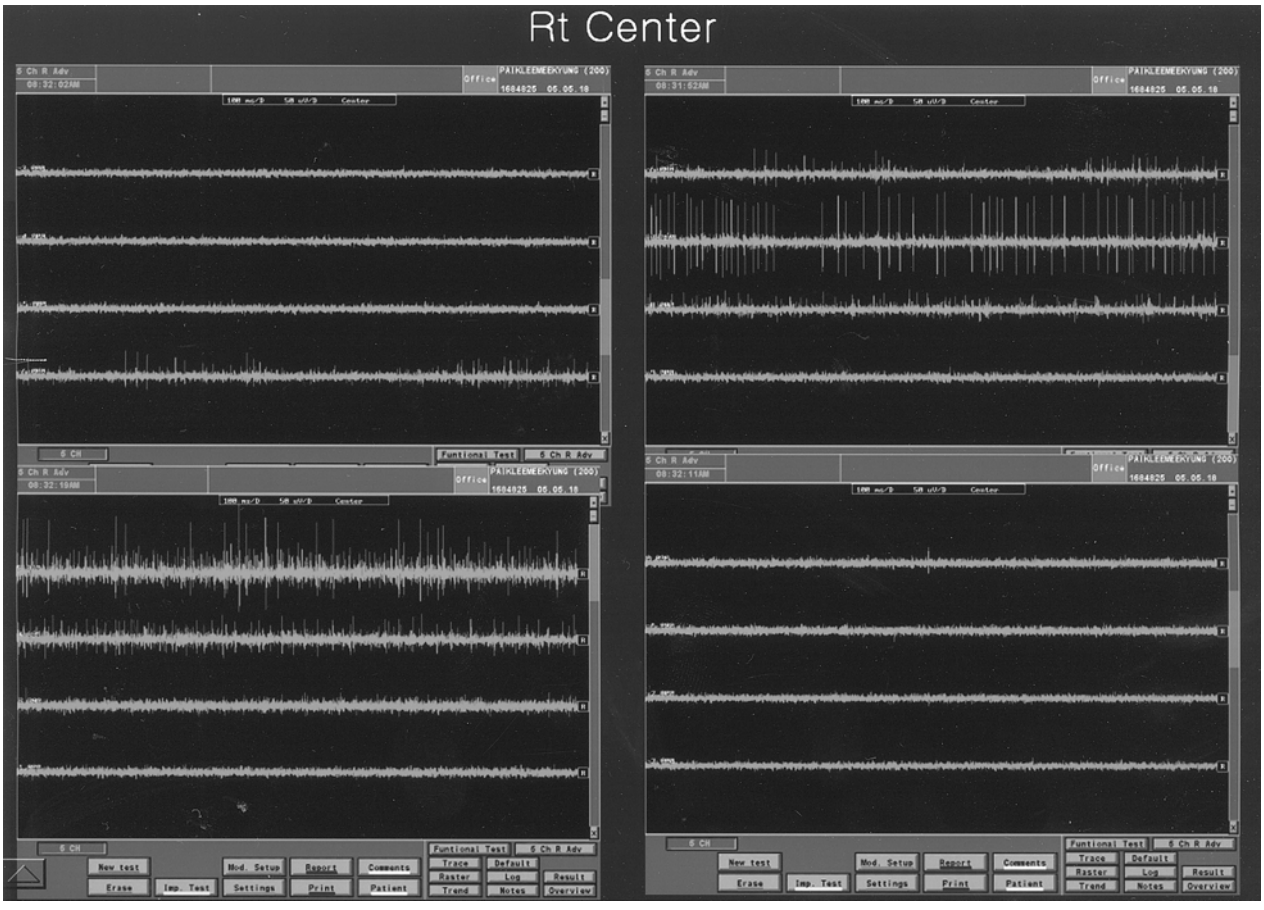

Fig. 3. Continuous microelectrode recording in Lead point 2

Theodosopoulos *et al.* [17] studied the location of 303 cells during 15 procedures for STN-DBS for Parkinson's disease. The dorsolateral part of the nucleus was the predominant location of the movement-related cells. Within this part of the nucleus, leg- and arm-related cells exhibited different locations. Leg-related cells occupied a relatively central location, whereas arm-related cells tended to populate the lateral part and the rostral and caudal poles of the nucleus.

The somatotopic organization of the skeletomotor territory of SNr is unclear. DeLong *et al.* [2] showed that five of seven arm-related cells recorded in a primate study were located ventrally and posteriorly with respect to orofacial cells. Leg-related activity has not been identified. There is little information on movement-related activity in the human substantia nigra [17]. On a parasagittal approach to the subthalamic nucleus at 55–60 degrees from the AC-PC plane, the typical operative trajectory passes along the anterior part of the thalamus, transverses the zona incerta, enters the subthalamic nucleus, and encounters the substantia nigra past the nucleus's ventral border. Thalamic cells recorded on this trajectory may demonstrate bursting or non bursting patters, with mean discharge rates of 15 ± 19 Hz and 28 ± 19 Hz, respectively [6]. High background activity, frequent multicellular recordings, and firing rates of 30–50 Hz are characteristic of subthalamic nucleus cells [17]. The discharge pattern is typically chaotic, with frequent irregular bursts and pauses [17]. The finding of movement-related activity confirms that the microelectrode is within the dorsolateral subthalamic nucleus, the presumed target area for subthalamic nucleus-Deep Brain Stimulation. In our study, the firing rate of 14–50 Hz was seen in subthalamic nucleus and finding of movement related activity of the dorsolateral subthalamic nucleus was checked. Motor symptoms are improved by the ''micro lesion'' effect associated with microelectrode recording mapping or DBS lead insertion [17].

In conclusion, the microelectrode recording of Neuro Trek and Lead point showed unique results of the typical subthalamic nucleus spike. Interest in the electrophysiology of the subthalamic nucleus is prompted by

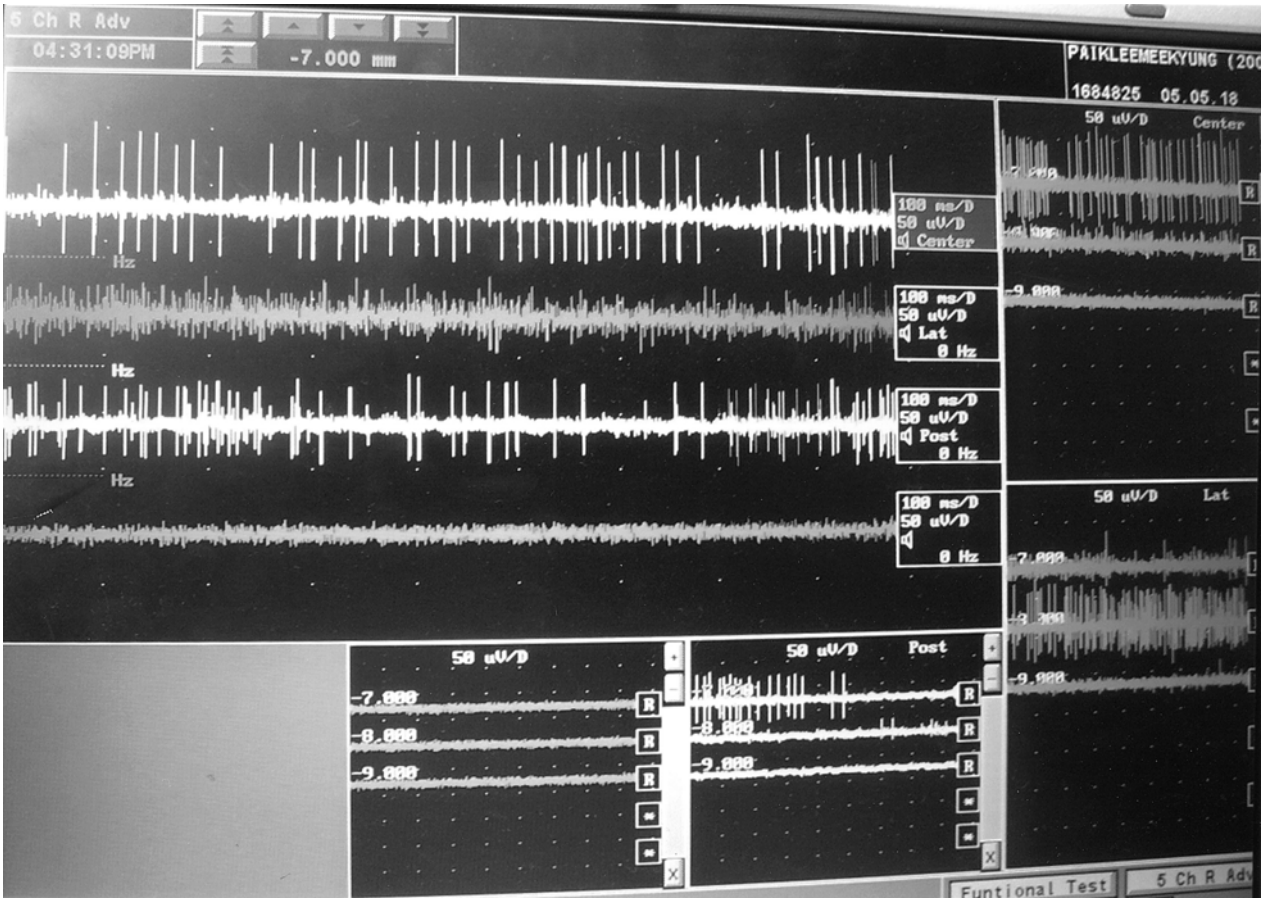

Fig. 4. Simultaneous microelectrode recording in STN ''BEN-GUN''

its increasing importance in the surgical treatment of Parkinsonism.

References

1. Bressand K, Dematteis M, Kahane P, Benazzouz A, Benabid AL (1998) High frequency stimulation of the subthalamic nucleus suppresses absence seizures in the rat: comparison with neurotoxic lesions. Epilepsy Res 31: 39–46
2. DeLong MR, Crutcher MD, Georgopoulos AP (1983) Relations between movement and single cell discharge in the substantia nigra of the behaving monkey. J Neurosci 3: 1599–1606
3. DeLong MR, Crutcher MD, Georgopoulos AP (1985) Primate globus pallidus and subthalamic nucleus: functional organization. J Neurophsiol 53: 530–543
4. DeLong MR, Crutcher MD, Georgopoulos AP (1983) Relations between movement and single cell discharge in the substantia nigra of the behaving monkey. J Neurosci 3: 1599–1606
5. Gielen FLH (2002) Simultaneous microelectrode recordings in STN ''BEN-GUN'' therapy and proceeding solution training, pp 23–29
6. Hutchison WD (1998) Neurophysiological identification of the subthalamic nucleus in surgery for Parkinson's disease. Ann Neurol 44: 622–628
7. Hutchison WD, Allan RJ, Opitz H, Levy R, Dostrovsky JO, Lang AE, Lozano M (1998) Neuro-physiologic identification of the subthalamic nucleus in surgery for Parkinson's disease. Ann Neurol 44: 622–628
8. Hutchison WD, Lozano AM (2000) Microelectrode recordings in movement disorder surgery. In: Lozano AM (ed) Movement disorder surgey. Karger, Basel, pp 103–117
9. Magarinos-Ascone C, Riva-Meana C, Figueiras-Mendez R (2000) Neuronal activity in the subthalamic nucleus in Parkinson disease. Rev Neurol 31(1): 66–71
10. Magnin M, Jetzer U, Morel A, Jeanmonod D (2001) Microelectrode recording and macrostimulation in thalamic and subthalamic MRI guided stereotactic surgery. Neurophysiol Clin 31(4): 230–238
11. Monakow KH, Akert K, Kunzle H (1978) Projections of the precentral motor cortex and other cortical areas of the frontal lobe to the subthalamic nucleus in the monkey. Exp Brain Res 33: 395–403
12. Nambu A, Takada M, Tokuno H (1996) Dual somatotopical representations in the primate subthalamic nucleus: evidence for ordered but reversed body-map transformations from the primary motor cortex and the supplementary motor area. J Neurosci 16: 2671–2683
13. Raeva SN, Lukashev A (1993) Unit activity in human thalamic reticularis neurons. II. Activity evoked by significant and non-significant verbal or sensory stimuli. Electroenceph Clin Neurophysiol 86: 110–122
14. Racva SN, Lukashev A, Lashin A (1991) Unit activity in human thalamic reticular nucleus. I. Spontaneous activity. Electroenceph Clin Neurophysiol 79: 133–140

15. Rodriguez MC, Guridi OJ, Alvarez L, Mewesk, Macias R, Vitek J, DeLong MR, Obeso JA (1998) The subthalamic nucleus and tremor in Parkinson's disease. Mov Disord 13 [Suppl] 3: 111–118
16. Slavis KV, Holsapple J (2004) Microelectrode techniques: equipment, components, and system. In: Zvi I, Kim JB (eds) Microelectrode recording in movement disorder surgery. Thieme, New York, pp 14–27
17. Theodosopoulos PV, Marks WJ, Christine C, Starr PA (2003) The locations of movement-related cells in the human Parkinson subthalamic nucleus. Mov Disord 18: 791–798
18. Wichmann T, Bergman H, Delong MR (1994) The primate subthalamic nucleus: I. Functional properties in intact animals. J Neurophysiol 72: 494–506
19. Welter ML, Houeto JL, Bonnet AM, Bejjani PB, Mesnage V, Dormont D, Navarro S, Cornu P, Agid Y, Pidoux B (2004) Effect of high-frequency stimulation on subthalamic neuronal activity in parkinsonian patients. Arch Neurol 61(1): 89–96

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Follow-up of bilateral subthalamic deep brain stimulation for Parkinson's disease

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Summary

Purpose. To demonstrate the effects of bilateral subthalamic deep brain stimulation (STN-DBS) in the treatment of Parkinson's disease (PD) after 4–45 months' follow-up.

Method. Between 04/01 and 12/04, 46 PD patients were operated on with bilateral STN-DBS. All of them were evaluated with Unified Parkinson's Disease Rating Scale (UPDRS) parts II–V before surgery and 4–45 months after surgery. The amelioration of miscellaneous symptoms and decrease of medication dose, respectively, were compared. Main side effects were observed.

Findings. After surgery, both the score of activities of daily living (ADL) and the UPDRS motor score decreased significantly ($p < 0.001$). Among the PD symptoms, tremor was improved best. Rigidity, bradykinesia, axial symptoms, facial expression and dyskinesia were all improved, although to a lesser extent, while speech was not improved. Medication dose was decreased significantly ($p < 0.001$). According to the time of follow-up, 4 groups were classified (4–12 months, 13–24 months, 25–36 months and 37–45 months group). ADL, UPDRS motor score and dyskinesia subscore improvement were compared among these groups. No significant difference existed. No life threatening complications occurred. Main side effects included hypophonia, dyskinesia, confusion, depression.

Conclusions. Bilateral STN-DBS is a satisfying surgical method for the treatment of advanced PD. It can improve the cardinal PD symptoms up to 45 months. Complications and side effects were rare and usually temporary or reversible.

Keywords: Deep brain stimulation; subthalamic nucleus; follow-up.

Introduction

In the past few years, deep brain stimulation (DBS) has become an accepted treatment modality for Parkinson's disease (PD) patients who experience disabling motor fluctuations and dyskinesia as a result of dopaminergic therapy, and some follow-up data have been published, including short-term follow-up for 3–6 months and long-term follow-up for up to 5 years. The selected targets varied from subthalamic nucleus (STN) to globus pallidus internus (GPi) [2, 4, 12, 14, 20]. The objective of our study was to demonstrate the effects of bilateral STN-DBS in the treatment of PD after 4–45 months' follow-up. To our knowledge, this is one of the several largest series study in this field.

Materials and methods

Patient selection

Forty six idiopathic PD patients were admitted to Beijing Tiantan Hospital between 04/01 and 12/04. There were 31 men and 15 women. Their age ranged from 42 to 78 years, averaging 63.8 ± 7.8 years. Average duration of PD until surgery was 11.31 ± 3.63 years (ranging from 4 to 18 years). Inclusion and exclusion criteria followed international recommendations (Core Assessment Program for Surgical International Therapies; CAPSIT). All cases had preserved levodopa effectiveness, but with severe motor fluctuations and dyskinesias and prolonged Off states. Hoehn-Yahr Scale of the patients before surgery was: Grade II: 10 cases, Grade III: 18 cases, Grade IV: 13 cases, Grade V: 5 cases. Before surgery, the Unified Parkinson's Disease Rating Scale (UPDRS) motor score, activities of daily living (ADL), dyskinesia were evaluated in both medication off and on states. Total equivalent dose of levodopa was calculated according to the accepted equivalence among different dopaminergic medications.

Surgical procedure

The surgical procedure coincided with those from other literature. Briefly, the patient was fixed with a Leksell stereotactic headframe on the morning of surgery and transferred to MRI suite to take MRI (3.0 Tesla) examination. The image data was then transferred to the Surgiplan workstation in the operation room. STN was 2–3 mm posterior to the midcommissural point, 12–13 mm lateral to the midplane of the third ventricle and 4–6 mm below the intercommissural line. The anatomical boundary of STN was easily distinguishable on the T2 and

Flair weighted images and the coordinates were calculated automatically by Surgiplan system. The patient was operated on under local anesthesia. Intraoperative microelectrode recording was used to verify the firing pattern of STN. Quadripolor electrodes (Medtronic Inc., electrode 3389) were implanted bilaterally in STN. Intraoperative physiological test ensured the appropriate response of the patient and no obvious adverse effect. Then under general anesthesia, implanted pulse generator (IPG, Medtronic Inc., Kinetra) was implanted subcutaneously in the subclavicular region. The stimulator started to work 2–3 weeks later and was programmed several times till the most ideal effects occurred.

Follow-up of patients

From 04/05 to 07/05, we carried out follow-up throughout China. The follow-up time ranged from 4 to 45 months, averaging 19.26 ± 8.35 months. The items of evaluation were the same as those before surgery, except that four states of the patient were assessed, including medication off/stimulation off ($Med_{off}/Stim_{off}$), medication off/stimulation on ($Med_{off}/Stim_{on}$), medication on/stimulation off ($Med_{on}/Stim_{off}$) state and medication on/stimulation on ($Med_{on}/Stim_{on}$). The equivalent dose of levodopa was also calculated.

Statistics

In comparison of ADL, UPDRS motor score and subscores, dyskinesia and levodopa equivalent daily dose (LEDD) in all patients, a paired *t* test was used. In comparison of their improvement after surgery among different time of follow-up, a one way ANOVA was firstly used. If significant difference existed, then an independent-samples *t* test was to be used. Normal distribution of all variables was verified before comparison. Statistics was processed using SPSS-12 for Windows.

Results

Efficacy of bilateral STN-DBS

Postoperatively, all patients showed an improvement in ADL, UPDRS motor score and subcores, as well as dyskinesia subscores. The values of these variables and their comparison were shown in Table 1.

Since both parts II and IV in UPDRS were interview-based, and some patients never turned off the stimulator in their daily life, so these data were collected only in $Stim_{on}$ states after surgery. Compared with the preoperative value, ADL was improved by 42.9% in Med_{off} state ($p < 0.001$) and 29.1% in Med_{on} state ($p < 0.001$) after surgery. UPDRS motor score was evaluated in two and four different states before and after surgery, respectively. We compared among the values in different states before and after surgery. In Med_{off} states, stimulation could improve total motor score from 49.2 ± 19.3 to 29.7 ± 13.7 ($p < 0.001$, improvement rate 39.58%). The comparison of total motor score between $Med_{off}/Stim_{on}$ and $Med_{on}/Stim_{off}$ states showed no difference ($p = 0.094 > 0.05$), which meant no efficacy difference between medication and stimulation alone. $Stim_{on}/Med_{on}$ could further improve motor symptoms by 32.25% compared to $Stim_{on}/Med_{off}$ state ($Stim_{on}/Med_{off}$ 29.7 ± 13.7, $Stim_{on}/Med_{on}$ 20.2 ± 13.6, $p < 0.001$).

In order to demonstrate the alleviation extent of different motor symptoms, we compared tremor, rigidity, bradykinesia, axial symptoms, facial expression and speech separately. Among all these symptoms, tremor (items 20, 21) was improved best. In Med_{off} state, stimulation improved tremor by 68.63%, Med_{on} further improved tremor by 67.65%. Rigidity (item 22), bradykinesia (items 23–26), axial symptoms (items 27–30) and facial expression (item 19) were also improved prominently, although to a lesser extent than tremor. In Med_{off} state, stimulation improved rigidity, bradykinesia, axial symptoms and facial expression by 52.09, 31.30, 24.07 and 14.76%. Medication further improved these symptoms by 41.69, 27.98, 25.89 and 18.99% respectively. In contrast, speech (item 18) subscore comparison between Med_{off} state before surgery and $Med_{off}/Stim_{on}$ state after surgery showed no difference. Dyskinesia (items 32–35) was chiefly induced by dopaminergic

Table 1. *ADL, UPDRS score and subscores, dyskinesia scores comparison before surgery and at the time of follow-up (mean ± SD)*

Article	Preop		Postop			
	Med_{off}	Med_{on}	$Med_{off}/Stim_{off}$	$Med_{off}/Stim_{on}$	$Med_{on}/Stim_{off}$	$Med_{on}/Stim_{on}$
UPDRS ADL	27.5 ± 11.2	13.4 ± 6.9	–	15.7 ± 8.1^{b}	–	9.5 ± 6.0^{b}
UPDRS motor	49.2 ± 19.3	33.2 ± 23.2	52.3 ± 17.5	29.7 ± 13.7^{d}	35.6 ± 23.7	20.2 ± 13.6^{d}
Tremor	10.8 ± 6.9	7.7 ± 6.9	12.8 ± 7.3	3.4 ± 4.0^{d}	7.0 ± 8.0	1.1 ± 2.1^{d}
Rigidity	7.9 ± 5.0	5.8 ± 5.3	6.5 ± 5.4	3.8 ± 4.1^{d}	5.1 ± 5.5	2.2 ± 3.4^{c}
Bradykinesia	17.2 ± 7.1	16.0 ± 7.8	21.2 ± 8.5	11.8 ± 5.8^{d}	13.0 ± 8.1	8.5 ± 5.9^{d}
Axial symptoms	7.0 ± 3.9	5.0 ± 2.7	7.2 ± 3.3	5.3 ± 3.2^{d}	5.4 ± 3.8	4.0 ± 3.2^{c}
Facial expression	2.1 ± 1.1	1.5 ± 1.3	2.1 ± 1.7	1.8 ± 1.0^{c}	1.7 ± 1.0	1.4 ± 1.1^{c}
Speech	1.9 ± 1.1	1.4 ± 1.0	1.8 ± 1.2	1.9 ± 0.9^{e}	1.6 ± 0.9	1.6 ± 0.9
Dyskinesia	–	3.6 ± 1.3	–	–	–	0.7 ± 1.0^{b}

Difference of ADL and dyskinesia between preoperative and postoperative states: $^{a}p < 0.05$, $^{b}p < 0.001$). Difference of UPDRS motor score and subscores between different states before and after surgery: $^{c}p < 0.05$, $^{d}p < 0.001$, $^{e}p > 0.05$.

Table 2. *UPDRS scores comparison among different time of follow-up after surgery. Comparison was among different groups in both $Med_{off}/Stim_{on}$ and $Med_{on}/Stim_{on}$ states*

Article	4–12 months ($n=11$)		13–24 months ($n=17$)		25–36 months ($n=10$)		37–45 months ($n=8$)	
	$Med_{off}/Stim_{on}$	$Med_{on}/Stim_{on}$	$Med_{off}/Stim_{on}$	$Med_{on}/Stim_{on}$	$Med_{off}/Stim_{on}$	$Med_{on}/Stim_{on}$	$Med_{off}/Stim_{on}$	$Med_{on}/Stim_{on}$
UPDRS ADL	39.7 ± 12.9	61.3 ± 21.1	46.8 ± 15.8	67.9 ± 23.1	43.3 ± 17.4	64.3 ± 20.3	42.7 ± 11.6	63.3 ± 22.6
UPDRS motor	40.5 ± 17.9	62.6 ± 21.1	38.1 ± 29.7	58.3 ± 26.2	38.1 ± 4.6	51.4 ± 7.0	44.3 ± 8.0	66.9 ± 14.8
Tremor	66.0 ± 26.5	84.2 ± 29.0	57.1 ± 43.6	90.8 ± 18.8	75.5 ± 23.7	87.8 ± 14.1	90.0 ± 20.0	97.5 ± 50.0
Rigidity	40.1 ± 39.6	71.8 ± 37.6	63.5 ± 42.8	65.2 ± 63.1	46.9 ± 32.1	57.2 ± 42.3	42.4 ± 33.5	60.2 ± 45.6
Bradykinesia	30.0 ± 21.4	57.1 ± 27.8	39.9 ± 30.4	49.1 ± 34.3	22.7 ± 7.4	38.4 ± 13.4	30.2 ± 19.5	51.6 ± 26.8
Axial symptoms	28.0 ± 29.5	45.8 ± 31.6	18.0 ± 24.8	41.3 ± 33.5	38.7 ± 7.3	43.9 ± 6.3	24.2 ± 17.1	59.6 ± 17.3
Facial expression	26.2 ± 39.5	31.6 ± 48.3	7.1 ± 18.9	46.4 ± 46.6	14.6 ± 17.2	29.2 ± 21.0	33.3 ± 47.1	45.8 ± 41.7
Speech	0.0 ± 34.0	14.5 ± 40.7	–33.3 ± 47.1	0.0 ± 0.0	13.5 ± 17.8	29.2 ± 21.0	20.8 ± 25.0	38.3 ± 43.3
Dyskinesia	–	78.3 ± 27.2	–	79.9 ± 20.1	–	83.3 ± 16.3	–	80.2 ± 19.3

medications, thus it was compared between Med_{on} state before surgery and $Med_{on}/Stim_{on}$ state after surgery. The result showed a dramatic improvement by 80.6%. Meanwhile, LEDD (Levodopa equivalent daily dose) was decreased by 34.1%, its value 747.5 mg/d and 492.5 mg/d before and after surgery. The diminution was significant ($p<0.001$). Four cases ceased to take any antiparkinson medication any more.

According to the follow-up time after surgery, the 46 patients in our series were divided into four groups: patients followed up between 4 to 12, 13 to 24, 25 to 36 and 37 to 45 months. We then compared ADL, UPDRS motor score and subscores, dyskinesia improvement in order to evaluate the long-term efficacy of STN-DBS. The results were shown in Table 2.

All variables in different groups were compared with one way ANOVA . In $Med_{off}/Stim_{on}$ state, there was no difference in both ADL and UPDRS motor score among different groups (ADL: $p=0.634$, UPDRS motor score: $p=0.856$). Comparison among different subitems of UPDRS motor score showed similar results (tremor: $p=0.637$, rigidity: $p=0.842$, bradykinesia: $p=0.570$, axial symptoms: $p=0.986$, facial expression: $p=0.384$, speech: $p=0.622$). In $Med_{on}/Stim_{on}$ state, there was no difference in ADL, UPDRS motor score and dyskinesia among different groups (ADL: $p=0.723$, UPDRS motor score: $p=0.698$, dyskinesia subscore: $p=0.564$). Comparison among different subitems of UPDRS motor score also showed no difference (tremor: $p=0.766$, rigidity: $p=0.880$, bradykinesia: $p=0.460$, axial symptoms: $p=0.853$, facial expression: $p=0.329$, speech: $p=0.712$). Based on the above results, we did not further compare variables between different group by independent-samples t test. In conclusion, the improvement of ADL, parkinsonian motor symptoms and dyskinesia by STN-DBS was kept stable for at least 45 months, whether in the Med_{on} or Med_{off} state.

Complications and side effects

In our series, there was no life threatening complications. Since postoperative MRI was not a routine examination, we could not exclude asymptomatic intracranial hematoma. Nonetheless, no symptomatic intracranial hematoma was encountered. Scalp ulceration due to lead abrasion occurred in 2 cases and was sutured subsequently. Side effects such as paraesthesia and eye movement disorder were usually transient and reversible. Seven cases complained of reversible hypophonia, accounting for 15.2% of all patients. Two patients had to stand up to dyskinesia when the parameters well controlled other parkinsonian symptoms. Adjustment of parameters led to disappearance of dyskinesia and recurrence of parkinsonian symptoms simultaneously. Other side effects included psychological disorders such as depression in 2 patients, confusion in 1 patient. Postoperative obesity was also complained in 3 patients although no accurate body weight comparison was available.

Discussion

During the past few year, STN-DBS has been used worldwide in the treatment of PD. Some published data are now available, thus the results can be compared among different medical centers. In our series, ADL was improved by 42.9% and 29.1% in medication off and on states, respectively. UPDRS motor score was improved by 39.58% in medication off states. Medication further improved another 32.35%. Dyskinesia was improved by 80.6% compared to it before surgery. LEDD was

reduced by 34.1% compared to that before surgery. As to the different motor symptoms, tremor was best improved by 68.63% in medication off state, followed in order by rigidity, bradykinesia, axial symptoms and facial expression, by 52.09, 31.30, 24.07 and 14.76%, respectively. Our results confirm the comprehensive efficacy of bilateral STN-DBS in the treatment of PD and demonstrate that combination of medication and STN-DBS could best improve motor symptoms. The results corroborate the outcome of other published studies. Previous studies showed motor disability improvement in the medication off state varied between 33 and 67% [2, 4, 6–8, 12, 14–17, 19, 20]. Reduction of the UPDRS part IV score varied between 80 and 92% [19]. The extent of diminution of LEDD ranged between 40 and 80.4% [9, 15, 17, 21]. The improvement of motor disability and dyskinesia in our series was within the range of other literature, while LEDD dimunition was not as ideal as other reports. We believe this is partly because the preoperative dose in our group is also lower than others, due to the insufficient medical therapy in our country. Although some authors [18, 19] completely replaced dopaminergic medication by STN-DBS in 50% of patients, only 4 patients in our group withdrew their medication completely. Thus we highly recommend the combination of medication and STN-DBS after surgery. We also compared the improvement of PD symptoms among different times of follow-up. No difference was present among the 4–12, 13–24, 25–36 and 37–45 months groups, confirming the long-term efficacy of STN-DBS. This is also in accordance with other reports.

The complications of STN-DBS surgery include device-related complications such as skin ulceration, lead fracture and displacement, as well as surgical complications, such as intracranial hematoma and infections. The absence of symptomatic intracranial hematoma in our series was attributed to careful manipulation during operation. Avoidance of sulcus in the electrode trajectories, prevention of CSF overdrainage, precise localization of the target to reduce repeating puncture were crucial. Microelectrode recording was routinely applied, with no obvious bleeding. Although theoretically the risk of bleeding was increased by microelectrode trajectories, the facilitation of localization made it worthy of utilization. In our group, 7 patients had hypophonia after surgery. Reduction of stimulating parameters could alleviate the symptom. Other authors have reported similar side effects, usually with a lower incidence [7, 21]. It may be caused by the current diffusion to the internal capsule. The relatively higher incidence of hypophonia in our series was due to electrode position. Another remarkable side effect in our series was DBS-related dyskinesia, which occurred in 2 patients. Although the incidence was rather low, it was very prominent and intolerable. Adjustment of parameters led to disappearance of dyskinesia and recurrence of parkinsonian symptoms simultaneously. Until the last follow-up, the appropriate parameter, medication and ideal outcome did not occur simultaneously in these patients. Many authors reported that stimulation-induced dyskinesia was a good predictive indicator of STN-DBS effectiveness and was reversible after reduction of stimulating parameters. However, the optimal parameter, medication and ideal outcome should be integrated together. Other side effects were usually psychiatric such as depression, confusion, and occurred in 2 and 1 patient in our series. The same problems have been widely discussed by other authors [10, 13]. The cause of postoperative depression is unclear. One explanation may be the addiction to dopaminergic treatment and subsequent reduction of medication dosages, with a negative affective withdrawal state. More attention should be paid to mood disorders after surgery.

Since the application of DBS in PD, GPi and STN have been the two most popular targets. Some clinical studies proved the efficacy of GPi-DBS in reducing off-period symptoms, dyskinesias, and motor fluctuation in advanced PD for 3–12 months. While a follow-up period of 5 years showed that although dyskinesia remained significantly reduced, the initial improvement of off-period motor symptoms and fluctuations gradually declined. Beneficial effects on ADL in the on- and off-period were lost after the first year [3, 5, 11]. Based on all these results, most authors believe that STN-DBS may be superior to GPi-DBS. Nonetheless, a recent randomized blinded pilot comparison of the safety and efficacy of STN and GPi stimulation in patients with advanced PD questions the above opinion. PD patients were randomized to implantation of bilateral GPi or STN stimulators. Off-period UPDRS motor scores, bradykinesia and LEDD were improved better by STN-DBS compared to GPi-DBS after 12 months, while dyskinesia was reduced better by GPi-DBS than by STN-DBS. Cognitive and behavioral complications were observed only in combination with STN stimulation [2]. In our opinion, these results might be caused by the relative short period of follow-up. Bilateral STN-DBS is still the first choice for advanced PD.

In conclusion, our study showed the high efficacy and safety of bilateral STN-DBS in the treatment of PD. It comprehensively improves all parkinsonian symptoms

including tremor, rigidity, bradykinesia, posture and gait instability. ADL of the patients is also improved. Medication is significantly reduced at the mean time, thus levodopa induced dyskinesia could be relieved. In most patients, combination of stimulation and medication leads to the best result. Complications and side effects are few and should be considered with caution. The efficacy of DBS is kept stable during long-term up of up to 45 months.

References

1. Anderson VC, Burchiel KJ, Hogarth P *et al* (2005) Pallidal vs. subthalamic nucleus deep brain stimulation in Parkinson disease. Arch Neurol 62: 554–560
2. Capecci M, Ricciuti RA, Burini D *et al* (2005) Functional improvement after subthalamic stimulation in Parkinson's disease: a non-equivalent controlled study with 12–24 month follow-up. J Neurol Neurosurg Psychiatry 76: 769–774
3. Durif F, Lemaire JJ, Debilly B *et al* (2002) Long-term follow-up of globus pallidus chronic stimulation in advanced Parkinson's disease. Mov Disord 17: 803–807
4. Ford B, Winfield L, Pullman SL *et al* (2004) Subthalamic nucleus stimulation in advanced Parkinson's disease: blinded assessments at one year follow-up. J Neurol Neurosurg Psychiatry 75: 1255–1259
5. Ghika J, Villemure JG, Fankhauser H *et al* (1998) Efficiency and safety of bilateral contemporaneous pallidal stimulation (deep brain stimulation) in levodopa-responsive patients with Parkinson's disease with severe motor fluctuations: a 2-year follow-up review. J Neurosurg: 89: 713–718
6. Houeto JL, Damier P, Bejjani PB *et al* (2000) Subthalamic stimulation in Parkinson's disease. A multidisciplinary approach. Arch Neurol 57: 461–465
7. Kumar R, Lozano AM, Kim YJ *et al* (1998) Double-blind evaluation of subthalamic nucleus deep brain stimulation in advanced Parkinson's disease. Neurology 51: 850–855
8. Lang AE, Lozano AM (1998) Parkinson's disease. New Engl J Med 339: 1044–1053 and 1130–1143
9. Lopiano L, Rizzone M, Bergamasco B *et al* (2001) Deep brain stimulation of the subthalamic nucleus: clinical effectiveness and safety. Neurology 56: 552–554
10. Moretti R, Torre P, Antonello RM *et al* (2003) Neuropsychological changes after subthalamic nucleus stimulation: a 12 month follow-up in nine patients with Parkinson's disease. Parkinsonism Relat Disord 10: 73–79
11. Olkmann J, Allert N, Voges J *et al* (2004) Long-term results of bilateral pallidal stimulation in Parkinson's disease. Annals Neurol 55: 871–875
12. Peppe A, Pierantozzi M, Bassi A *et al* (2004) Stimulation of the subthalamic nucleus compared with the globus pallidus internus in patients with Parkinson disease. J Neurosurg 101: 195–200
13. Piasechi SD, Jefferson JW (2004) Psychiatric complications of deep brain stimulation for Parkinson's disease. J Clin Psychiarty 65: 845–849
14. Rodriguez-Oroz MC, Zamarbide I, Guridi J *et al* (2004) Efficacy of deep brain stimulation of the subthalamic nucleus in Parkinson's disease 4 years after surgery: double blind and open label evaluation. J Neurol Neurosurg Psychiatry 75: 1382–1385
15. Romito L, Scerrati M, Contarino M *et al* (2002) Long-term follow up of subthalamic nucleus stimulation in Parkinson's disease. Neurology 58: 1546–1550
16. The Deep-Brain Stimulation for Parkinson's disease Study group (2001) Deep brain stimulation of the subthalamic nucleus or the pars interna of the globus pallidus in Parkinson's disease. N Engl J Med 345: 956–963
17. Thobois S, Mertens P, Guenot M *et al* (2002) Subthalamic nucleus stimulation in Parkinson's disease. Clinical evaluation of 18 patients. J Neurol 249: 529–534
18. Valldeoriola F, Pilleri M, Tolosa E *et al* (2002) Bilateral subthalamic stimulation monotherapy in advanced Parkinson's disease: long term follow-up of patients. Mov Disord 17: 125–132
19. Vingerhoets F, Villemure J, Temperli P *et al* (2002) Subthalamic DBS replaces levodopa in Parkinson's disease: two year follow up. Neurology 58: 396–401
20. Volkmann J, Allert N, Voges J *et al* (2004) Long-term results of bilateral pallidal stimulation in Parkinson's disease. Ann Neurol 55: 871–875
21. Volkmann L, Allert N, Voges J *et al* (2001) Safety and efficiency of pallidal or subthalamic stimulation in advanced PD. Neurology 56: 548–551

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Rapid subthalamic nucleus deep brain stimulation lead placement utilising CT/MRI fusion, microelectrode recording and test stimulation

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Summary

Subthalamic nucleus (STN) deep brain stimulation (DBS) has become an established treatment strategy for patients with medically refractory Parkinson's disease (PD). There are however numerous strategies employed for STN lead placement. Variations include method of STN localisation, use of microelectrode recording, number of microelectrode recording passes and time taken for the procedure. We describe a relatively simple and rapid technique of STN lead placement utilising CT/MRI image fusion, microelectrode recording and test stimulation.

The first 58 consecutive patients undergoing STN DBS were assessed pre- and post-operatively. UPDRS scores, medication use and any surgical complication were assessed.

Bilateral STN DBS was an efficacious treatment option for medically refractory PD. We have described a technique which can be performed with effect and low morbidity, and in a time which is well tolerated by patients.

Keywords: Deep brain stimulation; movement disorder; Parkinson's disease; subthalamic nucleus.

Introduction and aims

Subthalamic nucleus (STN) deep brain stimulation (DBS) has become an established treatment strategy for patients with medically refractory Parkinson's disease (PD). There are however numerous strategies employed for STN lead placement. Variations include method of STN localisation, use of microelectrode recording, number of microelectrode recording passes and time taken for the procedure. We describe a relatively simple and rapid technique of STN lead placement utilising CT/MRI image fusion, microelectrode recording and test stimulation, and present results of our first 58 consecutive patients.

Methods

Our series employs a uniform technique, used in two units encompassing three community hospitals (two in Brisbane, one in Sydney).

Procedure

Surgery is carried out in the "off" state. General anaesthesia (propofol) is induced in the radiology suite, and a CRW stereotactic frame affixed to the patient's head. After CT scanning the patient is transferred to the operating room and the headframe attached to the operating table. The frontal scalp is prepared and draped. A small bifrontal scalp flap is raised, and bifrontal burrholes are made, approximately 3 cm from the midline, but placed to avoid ventricular violation by the microelectrode or lead.

The ventromedial STN is directly targeted by visualisation on fused CT/MRI images. We use FLAIR sequences obtained on 1.5 or 3.0 Tesla scanners (usually obtained 1–2 days prior to surgery), with CT/MRI fusion carried out on Radionics, Stealth (Medtronics-Sofamor Danek) or BrainLab workstations. The target can be refined by additional visualisation on the Schaltenbrand atlases on the workstations, which can be "morphed" to fit the individual patient.

A 500 micron tungsten microelectrode (Fred Hayer Corporation) is passed via a microdrive attached to the headframe to 5 mm above the selected target. Microelectrode recordings are obtained at 1 mm steps through the STN to the substantia nigra (SN). Recordings are audibly and visually displayed on a Medtronics Leadpoint computer. White matter ("quiet areas") and characteristic STN and SN signals are confirmed.

With target confirmation by microelectrode recording, further confirmation is carried out by test stimulation. The 500 micron tip is withdrawn, and the distal outside sheath of the probe is used to provide stimulation at 130 Hz with a pulse width of 60 microseconds. The patient is examined for effect on clinical signs (dyskinesia, tremor, rigidity, bradykinesia) and absence of adverse effects.

After this step the microelectrode is withdrawn and the permanent DBS lead (Medtronic 3387) is placed through the same guidetube. The lead is fixed to the skull with a suture and bone cement.

After bilateral lead placement the patient is again anaesthetised. External connecting leads (Medtronic) are attached to the DBS leads and brought out through retroauricular stab incisions. The scalp wound is sutured and a head bandage applied.

Over the next several days lead placement in each STN is confirmed with an MRI scan (with appropriate safety protocols) and test stimulation via the external leads (Fig. 1). Internal pulse generators (Medtronic Soletra) are placed in infraclavicular pockets under general anaesthesia at logistically convenient time.

The first 58 consecutive patients undergoing STN DBS were assessed pre- and post-operatively. UPDRS scores, medication use and any surgical complication were assessed.

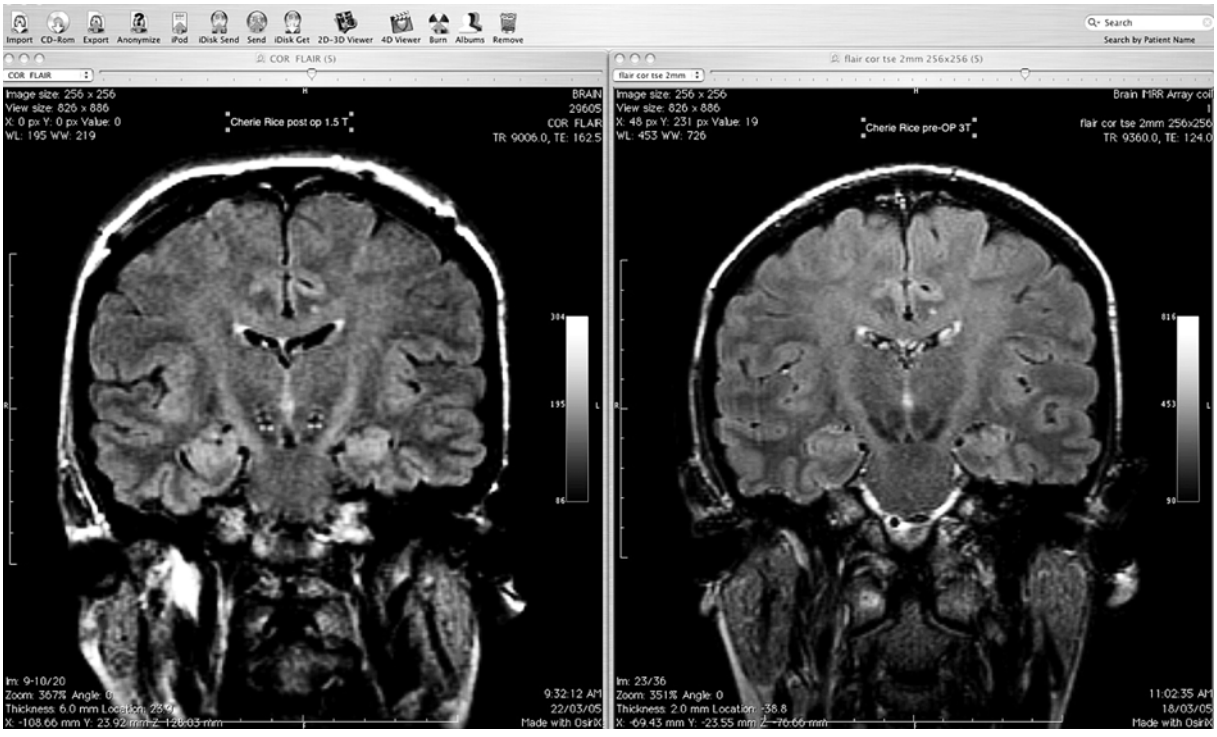

Fig. 1. Coronal FLAIR images showing STN – pre-operative image on right, post-operative image on left, showing satisfactory lead placement

Results

The 58 patients were assessed at 10 ± 6 months post-operatively. The patients underwent surgery during the period mid 2002–end 2004.

110/116 lead placements were performed with a single microelectrode pass. Average elapsed time from application of the stereotactic headframe to departing the operating room after bilateral lead insertion was 3 hours.

Table 1 demonstrates mean reduction in the unified Parkinson's disease rating scale (UPDRS) from best "on-medication" pre-operatively compared to best "on-stimulation" post-operatively, with or without medication.

Mean daily Levodopa equivalent in the population group was 1487 mg pre-operatively, and 471 mg post-operatively. This was a 68% reduction ($p < 0.0005$). 14/58 (24%) of patients became totally drug free, and another 17/58 (30%) were able to come off Levodopa.

Table 1

	Mean reduction	95% confidence interval	*P* value
UPDRS Part I	2.4 (75%)	1.7–3.1	<0.0005
II	4.3 (38%)	2.4–6.2	<0.0005
III	9.9 (44%)	7.7–12.2	<0.0005
IV	6.1 (88%)	4.7–7.4	<0.0005
Total score	22.7 (52%)	19.3–26.1	<0.0005

Table 2

Mortality – 0
Morbidity
5/116 (4%) leads not ideally placed and revised
Change in speech volume or fluency – 5 patients
Deep venous thrombosis – 1 patient
Symptomatic Haemorrhage – 0
Infection – 0

Complications are listed in Table 2.

Conclusion

Bilateral STN DBS was an efficacious treatment option for medically refractory PD. We have described a technique which can be performed with effect and low morbidity, and in a time which is well tolerated by patients.

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FDG-PET study of the bilateral subthalamic nucleus stimulation effects on the regional cerebral metabolism in advanced Parkinson disease

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Summary

The aim of the study was to evaluate the changes in regional cerebral metabolic rate of glucose (rCMRGlu) induced by bilateral subthalamic nucleurs (STN) stimulation in advanced Parkinson's disease (PD). ^{18}F-Fluorodeoxyglucose (FDG) PET data obtained before and one month after stimulation were analyzed with statistical parametric mapping (SPM). As a result of clinically effective bilateral STN stimulation, rCMRGlu increased in lateral globus pallidus (GP), upper brain stem, dorsolateral prefrontal cortex (DLPFC) and posterior parietal-occipital cortex, and decreased in the orbital frontal cortex and parahippocampus gyrus ($p < 0.001$). We conclude that the alleviation of clinical symptoms in advanced PD by bilateral STN stimulation may be the result of activation of both ascending and descending pathways from STN and of restoration of the impaired higher-order cortex functions.

Keywords: Parkinson's disease; subthalamic nucleus; deep brain stimulation; PET; ^{18}F-fluorodeoxyglucose.

Introduction

Stimulation of the subthalamic nucleus (STN), especially bilateral stimulation, may improve all cardinal motor signs of the Parkinson's disease (PD), and has become an effective treatment option in advanced medically intractable PD patients. However, the underlying mechanisms are still poorly understood. To elucidate the functional anatomic substrate involved in the clinical effect of STN stimulation, we investigated the changes in regional cerebral metabolic rate of glucose (rCMRGlu) with ^{18}F-fluorodeoxyglucose (FDG) PET examinations in PD patients under clinically effective bilateral STN stimulation.

Materials and methods

Patients

Five patients with insufficient symptom control by medication of advanced PD, all levodopa responsive, were selected for this study. The patients had a clear diagnosis of idiopathic PD with bilateral symptoms, disabling motor fluctuations despite adequate pharmacotherapy, no brain pathology as assessed by MRI, and no dementia symptoms. Bilateral STN electrodes (Medtronic model 3389; Medtronic, Minneapolis, MN) were implanted under local anesthesia using magnetic resonance imaging (MRI)-guided target identification and intraoperative macrostimulation. The electrodes were permanently connected to impulse generators (Soletra, Medtronic) and lead extensions in the same surgical session. The clinical characteristics of the patients are presented in Table 1.

Study design

Written informed consent was obtained from each subject before entering the study. All patients were scanned twice with FDG/PET. Preoperative imaging took place on the operation day just before mounting the frame and then one month after surgery. The patients fasted overnight prior to the scannings and antiparkinsonian medications had been discontinued at least 12 hrs. The STN stimulation was on at least 12 hrs prior to the postoperative PET imaging. Before the PET imaging, patients were rated according to the motor portion of Unified Parkinson's Disease Rating Scale (UPDRS III).

Positron emission tomography

The PET examinations were performed with an ECAT EXACT HR+ scanner (Siemens-CTI, Knoxville, USA) with the patient supine in resting state having the eyes covered and the ears plugged. In the three-dimensional mode, the scanner acquires oblique sinograms with a maximum cross-coincidence of ± 11 rings. A 10 min transmission scan with three rotating ^{68}Ge/^{68}Ga sources was performed for attenuation correction. The scanning was started 30 min after an intravenous bolus injection of 5 mCi of FDG and lasted for 10 min.

Data analysis

The data on rCMRGlu were analyzed with statistical parametric mapping (SPM 99, Wellcome Department of Cognitive Neurology, London, UK) implemented in Matlab 6.1 (Mathworks Inc., Sherborn, MA). The scans from each subject were aligned, stereotaxically normalized, and proportionately scaled. Metabolic measurements obtained pre- and postoperatively were compared on a voxel basis using the paired *t*-test option

Table 1. *Clinical characteristics of the PD patients 1 month after bilateral STN stimulation*

Patient no./sex/age	Disease duration yrs	UPDRS motor score (off drug)		Dopaminergic treatment (mg/24 h)	
		Pre-operation	1 month post-op	Pre-operation	1 month post-op
1/M/63	12	65	25	1200	1100
2/M/57	8	39	18	850	700
3/M/58	6	38	16	750	500
4/M/66	5.5	42	20	700	400
5/F/64	5	49	21	1650	800
Mean ± SD	7.3 ± 2.8	46.6 ± 11.1	20 ± 3.4	1030 ± 397.8	700 ± 273.9

Dopa equivalent: 100 mg L-dopa = 133 mg released L-dopa = 10 mg Bromocriptine = 1 mg Selegiline.

in SPM99. Operative changes were considered significant for $p < 0.001$ at cluster level over the entire volume in the brain analyzed.

Results

Clinical outcome

After one month of bilateral STN stimulation, UPDRS motor scores improved by 57.1% in the off medication state ($p < 0.005$). The mean dose of levodopa was decreased by 32% as compared to the preoperative condition.

Effects of bilateral STN stimulation on regional brain metabolism

Significant changes of the cerebral metabolic activity following clinically effective STN stimulation are summarized in Table 2 and Figs. 1 and 2. During the stimulation, FDG/PET showed a significantly *increased* rCMRGlu in the left lateral globus pallidus (GP), mid-

Table 2. *Areas with changes in resting-state cerebral metabolism in PD patients with bilateral STN stimulation*

Areas	Side (L/R)	Talairach coordinates			t score	*p*
		x	y	z		
Enhanced activation						
Occipital lobe,	L	−24	−78	−8	40.53	0.0001
Lingual gyrus (BA18)	R	4	−94	−14	26.89	0.0001
Parietal lobe,	L	−18	−54	56	9.02	0.001
Precuneus (BA7)	L	−12	−58	48	8.57	0.001
Middle frontal cortex (BA10)	R	46	52	−2	27.97	0.0001
Lateral globus pallidus	L	−14	−4	4	7.59	0.001
Brainstem, midbrain	R	14	−22	−18	8.04	0.001
	R	12	−26	−16	7.91	0.001
Reduced activation						
Inferior frontal cortex	R	42	20	10	8.71	0.001
(BA45, BA47)	L	−44	30	−14	14.31	0.001
Parahippocampal gyrus	L	−28	−4	−18	15.52	0.001

BA Brodmann area.

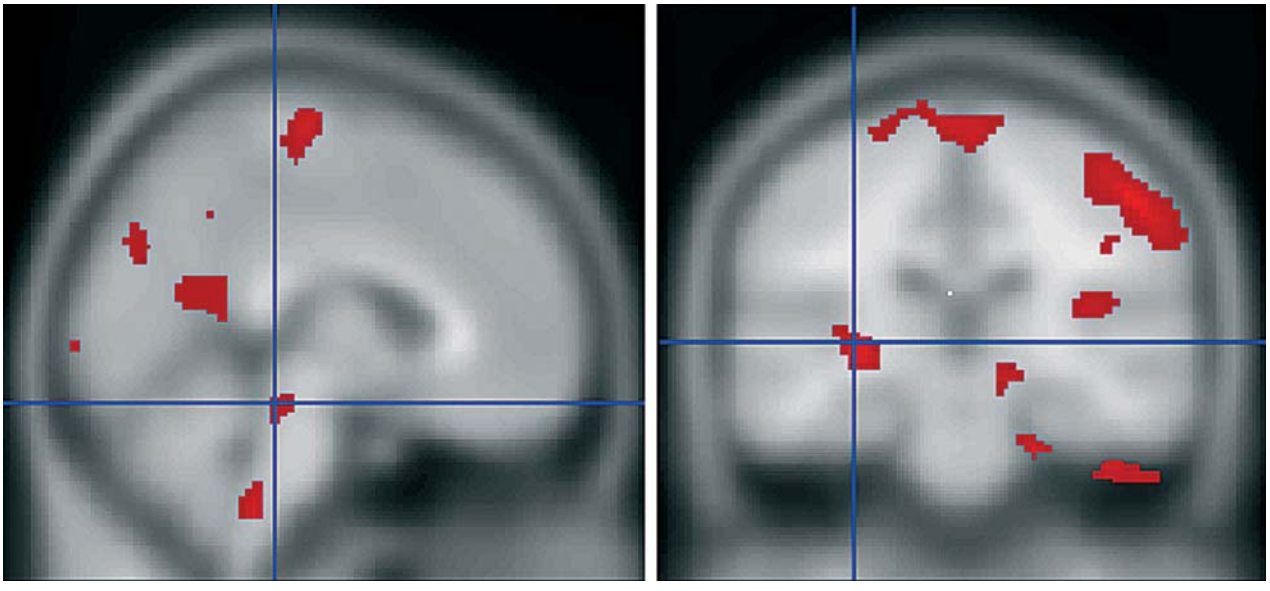

Fig. 1. Relative increase of activation in midbrain, globus pallidus and parietal-occipital cortex

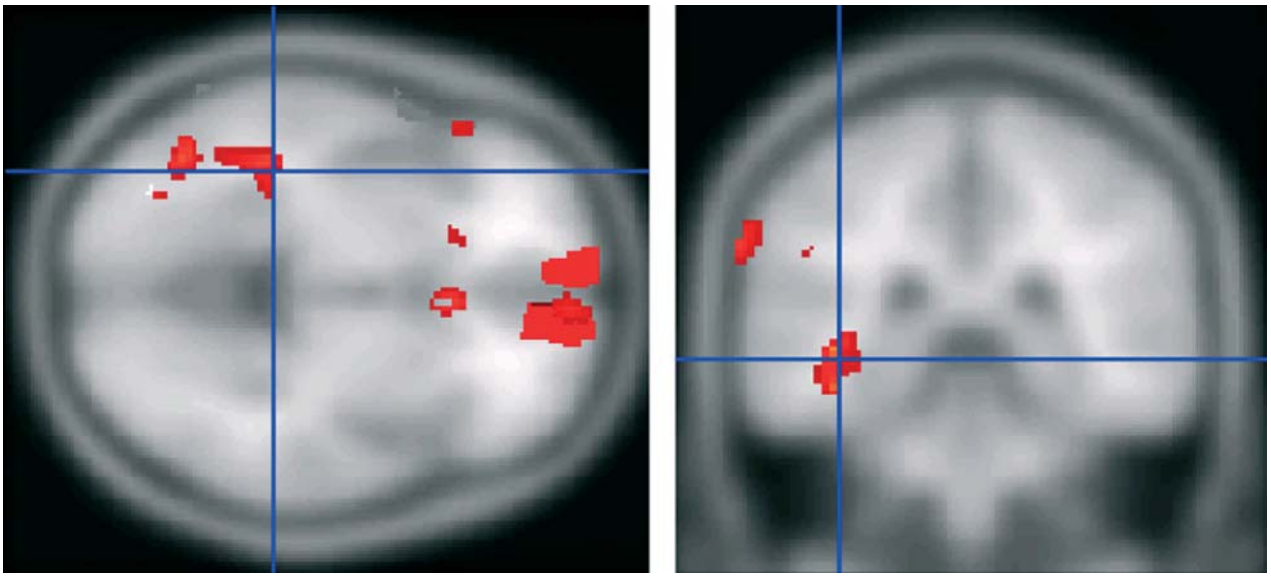

Fig. 2. Relative decrease of activation in orbital frontal cortex and left parahippocampus gyrus

brain, right dorsal lateral prefrontal cortex (DLPFC) and bilaterally in the posterior parietal-occipital cortex (BA7, 18). Significant *reductions* in glucose utilization were present in the bilateral orbitalfrontal cortices and in the parahippocampal gyrus.

Discussion

Resting state measurement of regional glucose utilization using FDG/PET can be applied for localizing the effects of stereotaxic surgical procedures on brain function. A previous resting state FDG/PET study has demonstrated that PD is characterized by lentiform, thalamic and pontine hypermetabolism associated with metabolic reductions in the lateral premotor, DLPFC and parietal-occipital association cortical regions [3].

The main findings in our study were the activation of lateral GP and the upper brain stem during bilateral STN stimulation. This is in contrast to the effects of subthalamotomy, which is reported to cause a decrease in the glucose metabolism in the lentiform nucleus, thalamus and the pons [6]. Since STN is reciprocally interconnected with lateral GP (GPe), the activation of that latter structure may be the result of orthodromatic activation of STN efferent or antidromatic activation of Gpe afferent fibers. This finding is consistent with a previous cerebral blood flow PET study after bilateral STN stimulation [7]. The activation of STN efferent destined to the pedunculopontine nucleus (PPN) in the upper brain stem is presumably part of the reason for the increased rCMRGlu in this area. Since the activation of PPN can improve akinesia, gait dysfunction and postural abnormalities as demonstrated in a primate PD model [4], this activation may also be a basis for the improvement of the axial symptoms in PD patients subjected to bilateral STN stimulation.

STN stimulation also influenced areas remote from the stimulation sites including DLPFC and bilateral parietal-occipital cortices. DLPFC is mostly involved in cognitive function such as motor planning or working memory, and the posterior parietal-occipital areas serve as higher-order sensory convergent areas for perception; they are also assumed to be involved in other higher brain functions such as self-initiated movements, which are typically impaired in PD patients [1, 2]. Clinically effective bilateral STN stimulation appears to restore these functionally deficient cerebral cortices in PD.

Another finding of STN stimulation was a decrease of FDG uptake in both orbitalfrontal cortices and the parahippocampal gyrus. Our findings may indicate that the depression observed in some patients treated with STN stimulation reflects a specific interference of the stimulation with limbic functions rather than being a sequel of postoperative levodopa reduction. In a previous neuropsychological study, it has been demonstrated that bilateral STN stimulation has a negative impact on various aspects of frontal executive capacity [5]. That observation may well correspond to our finding that the metabolism of the orbitalfrontal cortices is significantly reduced.

The present study demonstrates that STN high-frequency stimulation activates both ascending and de-

scending pathways resulting in either excitation or inhibition and in restoration of impaired higher-order cortex function in advanced PD patients.

Acknowledgements

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References

1. Bohnen NI, Minoshima S, Giordani B, Frey KA, Kuhl DE (1999) Motor correlates of occipital glucose hypometabolism in Parkinson's disease without dementia. Neurology 52: 541–546
2. Dubois B, Pillon B (1997) Cognitive deficits in Parkinson's disease. J Neurol 244: 2–8
3. Moeller JR, Nakamura T, Mentis MJ, Dhawan V, Spetsieres P, Antonini A, Missimer J, Leenders KL, Eidelberg D (1999) Reproducibility of regional metabolic covariance patterns: comparison of four populations. J Nucl Med 40: 1264–1269
4. Nandi D, Stein JF, Aziz TZ (2002) Exploration of the role of the upper brainstem in motor control. Stereotact Funct Neurosurg 78(3–4): 158–167
5. Saint-Cyr JA, Trepanier LL, Kumar R, Lozano AM, Lang AE (2000) Neuropsychological consequences of chronic bilateral stimulation of the subthalamic nucleus in Parkinson's disease. Brain 123: 2091–2108
6. Strafella AP, Dagher A, Sadikot AF (2003) Cerebral blood flow changes induced by subthalamic stimulation in Parkinson's disease. Neurology 60: 1039–1042
7. Su PC, Ma Y, Fukuda M, Mentis MJ, Tseng HM, Yen RF, Liu HM, Moeller JR, Eidelberg D (2001) Metabolic changes following subthalamotomy for advanced Parkinson's disease. Ann Neurol 50: 514–520

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Pain control

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Stimulation of primary motor cortex for intractable deafferentation pain

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Summary

To treat intractable deafferentation pains, we prefer stimulation of the primary motor cortex (M1). The methods of stimulation we utilize are electrical stimulation and repetitive transcranial magnetic stimulation (rTMS). In our department, we first attempt rTMS, and if this rTMS is effective, we recommend the patient to undergo procedures for motor cortex stimulation (MCS). A 90% intensity of resting motor threshold setting is used for rTMS treatment. In this study ten trains of 5 Hz rTMS for 10 seconds (50 seconds resting interval) were applied to the M1, S1, pre-motor and supplementary motor areas. Only M1 stimulation was effective for pain reduction in 10 of 20 patients (50%). Twenty-nine MCS procedures were performed by subdural implantation of electrodes, and in the case of hand or face pain, electrodes were implanted within the central sulcus (11 cases), because the main part of M1 is located in the central sulcus in humans. The success rate of MCS was around 63%, and seemed to be higher in cases of pain with spinal cord and peripheral origins, while it was lower in cases of post-stroke pain.

Keywords: Repetitive transcranial magnetic stimulation (rTMS); deafferentation pain; navigation; motor cortex; image-guided.

Introduction

Deafferentation pains are one of the most difficult types of pain to treat and are usually medically refractory. Only motor cortex stimulation (MCS) may provide pain relief in 50–75% of patients with deafferentation pains [6, 9, 11, 17]. Now, the primary motor cortex (M1) is a popular target for cortical stimulation as a method of treatment for medically refractory deafferentation pain [3, 5, 9, 11, 14, 15–17]. We have tried the sub-dural or intra-central sulcus implanting of electrodes to stimulate M1 more directly than is possible when using epidural techniques.

However, there have been few reports about the ability to relieve pain by stimulation of other adjacent cortical areas, for example, the postcentral gyrus (S1), supplementary motor area (SMA) and premotor area (preM). At our institute, we precisely applied repetitive transcranial magnetic stimulation (rTMS) to these areas, and compared the effectiveness of such treatments on pain relief.

Materials and methods

Patient profile

Twenty right-handed patients (14 males, 6 females, age ranging from 28 to 72 years) suffering from intractable deafferentation pain were treated with rTMS at Osaka University Hospital. There were 12 patients with post-stroke pain. Other origins of pain included two patients with spinal cord lesions, one with root avulsion, three with trigeminal nerve injuries, and two with peripheral nerve injuries. Patients had been administered with anti-convulsants, NSAIDs (non-steroidal anti-inflammatory drug), and anti-depressants and received psychological examinations and electroencephalogram (EEG) before rTMS to assess their potential for developing seizures. Informed consent was gained from all patients participating in this study, and approval was attained from the Ethics Committee of Osaka University Hospital.

Twenty-nine patients (25 males, 4 females, age ranging from 28 to 76 years) were treated with subdural or intra-central sulcus (11 cases) MCS. Of these, there were 16 patients with post-stroke pain. The other origins of pain included six brachial plexus injuries, three cases of phantom-limb pain, two cases of spinal cord lesions, one case of trigeminal neuropathic pain and one patient with pain related to pons injury. Five cases underwent both rTMS and MCS.

rTMS methods

rTMS was applied through a figure-of-eight coil which enabled a limited cortical stimulation, and which was connected to a MagPro magnetic stimulator (Medtronic Functional Diagnosis A/S, Skovlunde, Denmark). At first, the resting motor threshold (RMT) of muscle corresponding to the painful area was determined by stimulation of M1. A 90% intensity of the RMT was used for treatment. Ten trains of 5 Hz rTMS for 10 seconds (50 seconds resting interval) were applied to the M1, S1, preM and SMA areas at random. A total of 500 stimuli were applied once in two days and the stimulation was done twice for each target. Sham stimulation was applied using previously reported methods [19]. The protocol used was in accordance with guidelines for the safe use of rTMS [20]. We used the Brainsight™ Frameless Navigation system (Rogure Research Inc, Montreal, Canada) which monitored the position and direction of the coil, and the position of the patient's head

Table 1. *Summary of 5 cases who underwent both rTMS and MCS*

Case	Age	Sex	Diagnosis	Pain duration	Pain area	rTMS	MCS
1	71	M	lt thalamic hemorrhage	5 y	rt hand	poor	poor
2	62	M	lt thalamic hemorrhage	8 y	rt hand	excellent	good
3	28	M	lt trigeminal neuropathic pain	2 y	lt face	excellent	good
4	29	M	ruptured spinal AVM	6 y	rt foot	excellent	good
5	59	M	rt putaminal hemorrhage	16 y	lt foot	good	good

Five cases who underwent both rTMS and MCS are summarized. Only Case 1 showed pain relief by neither rTMS nor MCS. The other cases showed pain relief by both rTMS and MCS. There were good correlations between the results of rTMS and those of MCS.

by attaching trackers with reflectors recognizable by an optical position sensor camera similar to those used in other MRI guided navigation systems [1, 4, 10]. Fixation and placement of the TMS coil were achieved by an articulated coil holder.

Evaluation of pain relief and statistical analysis

We obtained measurements of visual analogue scale (VAS) and the short form of McGill Pain Questionnaire (SF-MPQ) before, during, and after stimulation (15, 30, 60, 90 and 180 minutes) for each of the targets (sham, preM, SMA, M1, S1) from 20 patients, and evaluated the effectiveness of stimulations with analysis of variance in a two-way layout (patient and time). Moreover, we investigated the significance among the pain intensities experienced in the following eight successive evaluations (pre-stimulation, intra-stimulation, post-stimulation, post-15 minutes, post-30 minutes, post-60 minutes, post-90 minutes, post-180 minutes) with Wilcoxon matched-pairs signed-ranks test.

Results

rTMS

All of the patients received full courses of navigation-guided rTMS and there was no transient or lasting side effects involving convulsions. They were not able to distinguish sham stimulation from real rTMS. Effective treatment was defined as a VAS improvement of more than 30%. Ten of 20 patients (50%) showed significant reductions in pain on the VAS with M1 stimulation. Stimulation of other areas (S1, SMA, preM) did not provide effective forms of pain relief. Effectiveness continued significantly for three hours ($p < 0.05$, Wilcoxon matched-pairs signed-ranks test).

There were no significant differences in SF-MPQ scores. In the patients with high SF-MPQ scores, who mentioned property of their own in many item of SF-MPQ, the results of VAS and SF-MPQ demonstrated similar tendencies. On the other hand, in the patients with low SF-MPQ scores, there were only slight score changes in spite of VAS score reductions.

MCS

Of the 29 patients, 18 (62%) showed good or excellent pain relief with MCS. Seven of the 11 cases (64%) who underwent electrode implant within the central sulcus showed good or excellent results. In the five cases who underwent both rTMS and MCS, four rTMS responders showed successful results of MCS, while one poor-responder was not successful (Table 1).

Discussion

Recently rTMS has been applied as a treatment method for psychiatric and neuro-degenerative diseases such as depression [7], dystonia [18], schizophrenia, Parkinson's disease, seizures and so on [21]. Based on experiences with MCS, rTMS is now beginning to be applied to cases of intractable deafferentation pain [8, 13].

According to PET and fMRI [2, 12] studies, several areas in the normal brain are thought to participate in the perception of pain. We have tried rTMS of the M1, S1, SMA and preM areas and have compared the effects on pain relief. Only M1 stimulation was effective in 50% of the patients. Why stimulation of the M1 area is effective in the treatment of pain is still under debate. Probably, the several areas of the brain activated by M1 stimulation relieve pain in a comprehensive manner [3, 12, 17]. The mechanism of pain relief by rTMS might be almost the same as that of electrical stimulation [8].

Previous reports have described implantation of epidural electrodes over the precentral gyrus [5, 9, 11]. Such an approach might not provide optimal pain relief since both the method and the area of test stimulation were restricted by a brief operative period under local anesthesia. Our subdural implant or implant within the central sulcus seems to be more effective than that of the epidural implant, because our methods make it possible to stimulate M1 more directly.

The five cases who underwent both rTMS and MCS showed good correlations with pain relief. There are some differences between the detailed stimulation of rTMS and MCS. We consider that rTMS can anticipate the results of MCS (Table 1).

In conclusion, only 5 Hz stimulation of M1 is able to reduce intractable deafferentation pain in approximately one out of two patients. The pain reduction continued significantly for three hours. Today, rTMS may be a good predictor of MCS efficacy, and thus, we consider that MCS can be recommended to the patients with good results of rTMS. In the future, rTMS may take over from MCS as a treatment of deafferentation pain.

References

1. Boroojerdi B, Foltys H, Krings T, Spetzger U, Thron A, Topper R (1999) Localization of the motor hand area using transcranial magnetic stimulation and functional magnetic resonance imaging. Clin Neurophysiol 110: 699–704
2. Coghill RC, Sang CN, Maisog JM, Iadarola MJ (1999) Pain intensity processing within the human brain: a bilateral distributed mechanism. J Neurophysiol 82: 1934–1943
3. Garcia-Larrea L, Peyron R, Mertens P, Gregoire MC, Lavenne F, Le Bars D, Convers P, Mauguiere F, Sindou M, Laurent B (1999) Electrical stimulation of motor cortex for pain control: a combined PET-scan and electrophysiological study. Pain 83: 259–273
4. Herwig U, Schonfeldt-Lecuona C, Wunderlich AP, von Tiesenhausen C, Thielscher A, Walter H, Spitzer M (2001) The navigation of transcranial magnetic stimulation. Psychiatry Res 108: 123–131
5. Katayama Y, Yamamoto T, Kobayashi K, Kasai M, Oshima H, Fukaya C (2001) Motor cortex stimulation for post-stroke pain: comparison of spinal cord and thalamic stimulation. Stereotact Funct Neurosurg 77: 183–186
6. Katayama Y, Yamamoto T, Kobayashi K, Oshima H, Fukaya C (2003) Deep brain and motor cortex stimulation for post-stroke movement disorders and post-stroke pain. Acta Neurochir [Suppl] 87: 121–123
7. Kimbrell TA, Little JT, Dunn RT, Frye MA, Greenberg BD, Wassermann EM, Repella JD, Danielson AL, Willis MW, Benson BE, Speer AM, Osuch E, George MS, Post RM (1999) Frequency dependence of antidepressant response to left prefrontal repetitive transcranial magnetic stimulation (rTMS) as a function of baseline cerebral glucose metabolism. Biol Psychiatry 46: 1603–1613
8. Lefaucheur JP, Drouot X, Menard-Lefaucheur I, Zerah F, Bendib B, Cesaro P, Keravel Y, Nguyen JP (2004) Neurogenic pain relief by repetitive transcranial magnetic cortical stimulation depends on the origin and the site of pain. J Neurol Neurosurg Psychiatry 75: 612–616
9. Meyerson BA, Lindblom U, Linderoth B, Lind G, Herregodts P (1993) Motor cortex stimulation as treatment of trigeminal neuropathic pain. Acta Neurochir [Suppl] 58: 150–153
10. Neggers SF, Langerak TR, Schutter DJ, Mandl RC, Ramsey NF, Lemmens PJ, Postma A (2004) A stereotactic method for image-guided transcranial magnetic stimulation validated with fMRI and motor-evoked potentials. Neuroimage 21: 1805–1817
11. Nguyen JP, Keravel Y, Feve A, Uchiyama T, Cesaro P, Le Guerinel C, Pollin B (1997) Treatment of deafferentation pain by chronic stimulation of the motor cortex: report of a series of 20 cases. Acta Neurochir [Suppl] 68: 54–60
12. Peyron R, Laurent B, Garcia-Larrea (2000) Functional imaging of brain responses to pain. A review and meta-analysis. Neurophysiol Clin 30: 263–288
13. Pleger B, Janssen F, Schwenkreis P, Volker B, Maier C, Tegenthoff M (2004) Repetitive transcranial magnetic stimulation of the motor cortex attenuates pain perception in complex regional pain syndrome type I. Neurosci Lett 356: 87–90
14. Rainov NG, Heidecke V (2003) Motor cortex stimulation for neuropathic facial pain. Neurol Res 25: 157–161
15. Saitoh Y, Shibata M, Hirano S, Hirata M, Mashimo T, Kato A, Yoshimine T (2000) Motor cortex stimulation for central and peripheral deafferentation pain. J Neurosurg 92: 150–155
16. Saitoh Y, Kato A, Ninomiya H, Baba T, Shibata M, Mashimo T, Yoshimine T (2003) Primary motor cortex stimulation within the central sulcus for treating deafferentation pain. Acta Neurochir [Suppl] 87: 149–152
17. Saitoh Y, Osaki Y, Nishimura H, Hirano S, Kato A, Hashikawa K, Hatazawa J, Yoshimine T (2004) Increased regional cerebral blood flow in the contralateral thalamus after successful motor cortex stimulation in a patient with poststroke pain. J Neurosurg 100: 935–939
18. Siebner HR, Filipovic SR, Rowe JB, Cordivari C, Gerschlager W, Rothwell JC, Frackowiak RS, Bhatia KP (2003) Patients with focal arm dystonia have increased sensitivity to slow-frequency repetitive TMS of the dorsal premotor cortex. Brain 126: 2710–2725
19. Tamura Y, Okabe S, Ohnishi T, N Saito D, Arai N, Mochio S, Inoue K, Ugawa Y (2004) Effects of 1-Hz repetitive transcranial magnetic stimulation on acute pain induced by capsaicin. Pain 107(1–2): 107–115
20. Wassermann EM (1998) Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5–7, 1996. Electroenceph Clin Neurophysiol 108: 1–16
21. Wassermann EM, Lisanby SH (2001) Therapeutic application of repetitive transcranial magnetic stimulation: a review. Clin Neurophysiol 112: 1367–1377

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Fifteen year experience of intrathecal baclofen treatment in Japan

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Summary

Intrathecal baclofen administration is a fully established treatment for severe spasticity. However, it is scarcely known that Baclofen, an agonist of GABA-B receptor, has other potential effects on pain, restoration coma, dystonia, tetanus, and hypothalamic storm. Sporadic episodes of dramatic recovery from persistent vegetative state are reported after intrathecal administration of baclofen. There are also reports on the use of baclofen for neuropathic pain including poststroke central pain syndrome. Baclofen is also used for control of dystonia due to cerebral palsy or reflex sympathetic dystrophy. On the other hand, epidural spinal cord stimulation has been used for pain, spasticity, dystonia, or attempt to improve deteriorated consciousness, though the effects seem variable and modest. Similarity between baclofen and spinal cord stimulation is interesting in that both involve the spinal GABAergic system. Based on the 15-year personal experience of intrathecal baclofen, I would stress importance of this treatment not only for spasticity but also for other difficult neurological disorders.

Keywords: Intrathecal baclofen; pain; dystonia.

It was more than 15 years ago that the first author became interested in neurosurgical management of spasticity, when almost no neurosurgeons in Japan knew about neurosurgical management of spasticity. During my fellowship study in Birmingham U.K. from 1988, my great mentor, Professor Hitchcock used to perform stereotactic dentatotomy for various kinds of spasticity. Although the effect of dentatotomy was transient, I observed many instances of dramatic immediate changes after relief of severe spasticity. This was the main reason I realized the importance of neurosurgical management of spasticity. After coming back to Japan, because baclofen for intrathecal use was not available, I personally imported the medication from Basel, Switzerland, and started trial bolus injection mainly to patients with post cerebrovasular accidents. Implantable pumps for chronic treatment were not available, but even with bolus injections. I noticed a variety of neurological changes from careful clinical observation.

One day, in the early 90s, I injected baclofen to a patient with foot spasticity after a stroke. The patient also had poststroke dysesthetic pain, and to my big surprise, the patient reported not only relief of spasticity but also the pain, which I could not believe in the beginning. In the same room of the ward, there was another patient with poststroke central pain who had undergone thalamic deep brain stimulation and motor cortex stimulation without remarkable benefit. This patient eagerly asked me to inject baclofen as a trial case. I hesitated and explained the difference of indication, but the patient insisted on trying, and finally I did. Again, it worked as shown in Fig. 1. I did not tell the patient the possible time course of drug effect, but the time curve of pain relief was compatible with bolus intrathecal baclofen for spasticity. Since then, I investigated the effect of bolus baclofen injection on various kinds of neuropathic pain.

Analgesic effect of baclofen is not widely known, though baclofen is the second choice drug for idiopathic trigeminal neuralgia. In clinical studies, intrathecal baclofen, of course, relieves muscle spasm pain, which is generally believed secondary to relief of spasticity. However, there have been some clinical reports concerning pain relief with intrathecal baclofen. Herman *et al.* [3] reported that central pain caused by spinal lesions is successfully controlled with lumbar intrathecal baclofen and obviously this is not the secondary effect. In their report, a patient even with a C3 lesion experienced relief of pain in the leg. I also reported that intrathecal baclofen effectively suppresses even poststroke central pain [5]. Such baclofen analgesia as in patients with central pain of spinal origin can be explained by suppression of the abnormal neuronal activities in the spinal posterior horn. Baclofen analgesia is not mediated through the endogenous opiate system. The neural structures rostral to

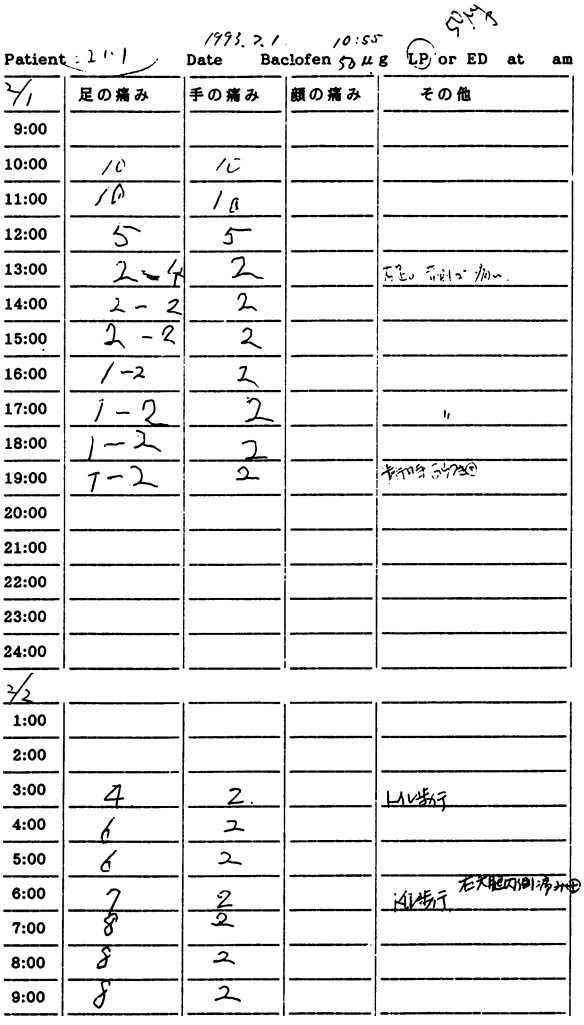

Fig. 1. Pain relief after intrathecal injection of baclofen. Baclofen was injected at 10:55 am and pain in the leg became 2/10 after 4 hours, and the effect on arm pain was still present on the following morning. Pain score was assessed by the patient

the medulla and caudal to the midbrain are necessary for the analgesic effect of baclofen. These findings suggest that there is an ascending pain control system from the spinal cord to the pons that is not mediated by the opiate system. Because baclofen acts on GABA-B receptor sites that are present in high concentration in the spinal dorsal horn, GABA may be the mediator of this pain control system. It has been reported that GABA is released by electrical spinal cord stimulation [2, 4], which technique has been widely used for pain relief. This further supports the importance of the GABAergic system in pain mechanism [8].

In 1995, I was asked to accept a patient from Kyushu area (900 km from Tokyo). The patient was a young boy who had become bed-ridden after severe traumatic brain injury. I had no idea what to do. When I first saw him, he was severely tetra-spastic, unconscious, and in so-called vegetative state. I desperately asked my residents to inject baclofen through a lumbar tap every day for at least one month. Then, to everyone's big surprise, the boy woke up after 25 injections, started talking, and eating by himself. Six months later, he returned home on foot (Fig. 2). Ten years from then, he is now a high school student. The recovery from vegetative state was dramatic [7].

There are some communications [Becker 1996, Meythaler 1996 and others] that they also experienced dramatic recovery of consciousness after intrathecal administration of baclofen. It is known that, in cerebral palsy children, selective dorsal rhizotomy and resultant relief of leg spasticity, it may show subsequent positive effects on higher brain functions. The effect of baclofen on persistent vegetative state may thus be secondary, but the effects in some limited cases are so dramatic that we have to consider the primary role of baclofen on disturbed consciousness. It is known that baclofen improves conduction in demyelinated axons and therefore intrathecal baclofen may accelerate the repair of diffuse axonal injury. Spinal cord stimulation has been used in the hope of recovery from persistent vegetative state, and in some cases, it is really effective. Thus, spinal cord stimulation and baclofen are also similar in terms of recovery from persistent vegetative state.

Spinal cord stimulation used to be reported as effective treatment of dystonia, though the results were not always uniform [10]. Intrathecal baclofen has been introduced for the treatment of generalized dystonia due to cerebral palsy or of unknown etiology, and the results seem promising [1]. It also opened a new therapeutic option for dystonia and pain in reflex sympathetic dystrophy that is refractory to most treatment [9]. Spinal cord stimulation is regarded as a choice of surgical treatment of reflex sympathetic dystrophy. Cerebral blood flow Spinal cord stimulation increases cerebral blood flow through unknown mechanisms not related with increased sensory input. The stimulation has been tried in ischemic stroke or vasospasm after subarachnoid hemorrhage. To our knowledge, there is no report on cerebral blood flow and baclofen in clinical setting, while we have experimental data on cerebral blood flow that increased following intrathecal administration of baclofen.

This year, the Government of Japan finally approved intrathecal baclofen and implantable pumps after 29 cases of clinical trial. They had requested us to perform high-cost domestic clinical trials despite the fact that several thousand patients have been benefiting every

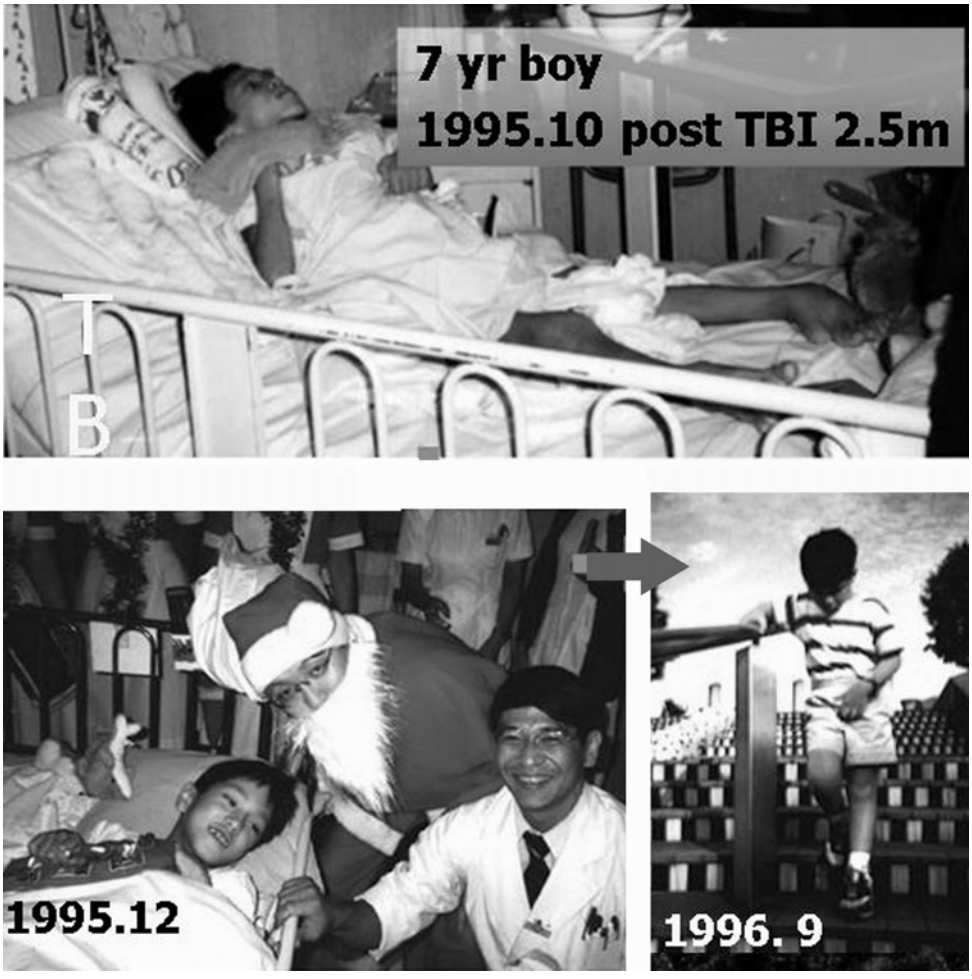

Fig. 2. Tetraspastic unconscious boy after traumatic brain injury. Intrathecal baclofen was used to relieve spasticity, and consciousness dramatically improved

year from this treatment in many other countries. Because of such political delay, I learnt a lot more on the action of baclofen and various aspects of intrathecal medical treatment.

References

1. Albright AL, Barry MJ, Shafton DH, Ferson SS (2001) Intrathecal baclofen for generalized dystonia. Dev Med Child Neurol 43: 652–657
2. Cui JG *et al* (1996) Effects of spinal cord stimulation on touch evoked allodynia involve GABAergic mechanisms. Pain 66: 287–295
3. Herman RM, D'Luzansky SD, Ippolito R (1992) Intrathecal baclofen suppresses central pain in patients with spinal lesions. Clin J Pain 8: 338–345
4. Stiller CO *et al* (1996) Release of GABA in the dorsal horn and suppression of tactile allodynia by spinal cord stimulation in neuropathic rats. Neurosurgery 39: 367–375
5. Taira T, Kawamura H, Tanikawa T, Iseki H, Takakura K (1994) Spinal intrathecal baclofen suppresses central pain after a stroke. J Neurol Neurosurg Psychiatr 57: 381–386
6. Taira T, Kawamura H, Tanikawa T *et al* (1995) A new approach to the control of central deafferentation pain. Acta Neurochir (Wien) 64: 136–138
7. Taira T, Kawamura H, Tanikawa T *et al* (1997) Dramatic recovery of consciousness after spinal intrathecal administration of baclofen in patients with severe head injury. Treatment Coma 5: 127–134
8. Taira T, Hori T (2000) The contemporary role of neurosurgeons in the management of intractable pain. In: Yanagida H *et al* (eds) Management of pain, a world perspective. Monduzzi, pp 201–204
9. van Hilten BJ, van de Beek WJ, Ho JI, Voormolen JH, Delhaas EM (2000) Intrathecal baclofen for the treatment of dystonia in patients with reflex sympathetic dystrophy. N Engl J Med 343: 625–630
10. Waltz JM, Davis JA (1983) Cervical cord stimulation in the treatment of athetosis and dystonia. Adv Neurol 37: 225–237

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Electrical stimulation of the anterior cingulate cortex in a rat neuropathic pain model

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Summary

Background. Electrical stimulation is currently employed to treat several neurological conditions, including pain and Parkinson's disease. It is one of several minimally invasive alternatives to drug treatments for painful conditions. A number of studies have shown that the anterior cingulate cortex (ACC) plays an important role in the processing of pain and pain modulation. The purpose of this study is to investigate these neuropathic pain-relieving effects by delivering electrical stimulation into the ACC of rat models.

Methods. Following the approval of the AAALAC and the Guidelines and Regulations for Use and Care of Animals in Yonsei University, rats were subjected to surgery under pentobarbital anesthesia (50 mg/kg, i.p.) to produce neuropathic pain. Electrodes were bilaterally implanted into the ACC with a metal holder for the electrical stimulation. The effect of the electrical stimulation of the ACC on the rat neuropathic pain model was measured by the von Frey test.

Findings. The effect of electrical stimulation of the ACC on neuropathic pain was shown during stimulation at 30, 40, 50, and 60 min, and at 10 min after stimulation. In the pain ACC stimulation group, the response of mechanical allodynia was significantly reduced during the time of ACC electrical stimulation.

Conclusion. The mechanical allodynia of the neuropathic pain could be modulated by ACC electrical stimulation.

Keywords: Electrical stimulation; anterior cingulate cortex (ACC); pain modulation; neuropathic pain.

Introduction

Electrical stimulation is currently used to treat several neurological conditions, including pain and Parkinson's disease [25]. It is one of the several minimally invasive alternatives to drug treatments for painful conditions [20]. In adult patients, the deep brain electrical stimulation of the thalamic nuclei helps to alleviate severe pain [25]. Many animal studies have demonstrated the inhibitory influences that electrical stimulation of the nervous system can have on pain transmission [9].

Although both its mechanisms of action and clinical effects are subjects of controversy, electrical stimulation at various sites in the central nervous system has been shown to induce analgesia, and is currently used as a therapy for chronic refractory deafferentation pain [18]. Precentral gyrus stimulation has analgesic effects for thalamic pain and trigeminal neuropathic pain [15, 24]. The electrical stimulation of the nucleus ventrocaudalis (Vc) of the thalamus is used to reduce chronic pain [22].

To control the pain, there are various target positions for electrical stimulation, according to the various pain mechanisms. A number of studies have shown that the anterior cingulate cortex (ACC) plays an important role in the processing of pain and pain modulation. Animal and human studies have indicated that the ACC mediates the pain-modulating circuitry, nociceptive processing [2, 10], arthritic pain [8], pain-related memory acquisition [17], unpleasantness [23], and aversion [14]. Single neurons of the ACC respond selectively to painful thermal and mechanical stimuli, supporting a role for the ACC in pain perception [11]. Also, the ACC is a part of the limbic system, and its functional relationship to emotional and motivational processes has been delineated [5]. However, at this time, the effects of electrical brain stimulation in the ACC on neuropathic pain are not well known.

In the present study, we will report on the neuropathic pain-relieving effect of the electrical brain stimulation of the ACC on the rat pain models. Also, we will introduce newly developed devices and operation methods.

Materials and methods

Experimental subjects

Experiments were performed on adult male Sprague-Dawley rats (180–200 g, Daehan Biolink Co. LTD., Eumsung, Korea). The animals were maintained in four groups, in plastic cages with soft bedding under a 12/12 h light-dark cycle (light cycle: 8:00 AM–8:00 PM), in facilities fully accredited by the AAALAC (Association for Assessment and Accreditation of Laboratory Animal Care). Temperature ($22 \pm 2\,^{\circ}C$) and humidity ($50 \pm 10\%$) were controlled to be constant. Food and water were available *ad libitum*. The care and use of laboratory animals in this experiment were based on the Guidelines and Regulations for Use and Care of Animals in Yonsei University.

Surgical procedures

The rat neuropathic pain model was prepared according to the methods described by Lee *et al.* [13]. Under pentobarbital anesthesia (50 mg/kg, i.p.), a segment of the sciatic nerve was exposed between the midthigh level and the popliteal fossa by skin incision and blunt dissection through the biceps femoris muscle. The three major divisions of the sciatic nerve (the tibial, sural, and common peroneal nerves) were clearly separated by individual perineurium. Neuropathic injury was induced by the tight ligation and cutting of the left tibial and sural nerves, leaving the common peroneal nerve intact. Complete hemostasis was confirmed, and the wound was closed with muscle and skin sutures.

Electrical stimulator

We used newly developed, small-sized portable stimulators to generate the voltage stimulus pulses (Fig. 1A). The main chip of the stimulator was an SX18AC microcontroller from Scenix. Stimulation parameters, such as duration and stimulation rate, could be changed with PC-based software (Fig. 1B). The parameters were stored in the internal ROM (Read Only Memory) of a chip through the RS-232C serial communication port. The amplitude of the stimulation voltage was controlled by the precision potentiometer. By adjusting the knob position of the potentiometer, the output voltage could be controlled from 0 to 4.5 V.

Finally, the stimulator was connected to the stimulation electrodes through the percutaneous connector that was the terminal of the subcutaneously implanted extension cable.

Implantation of anchor, electrode, and cable

We designed a unique metal anchor that was made of biocompatible stainless steel to fix the stimulation electrodes and to minimize infections and inflammations in the rats (Fig. 2A). With the anchor, we could close the scalp and reduce the size of the scar after implantation of the stimulation electrodes and extension cable. Therefore, we could stably maintain the experimental conditions for a long time. Under pentobarbital anesthesia (50 mg/kg, i.p.), a metal anchor was fixed on each skull with screws.

We used tungsten electrodes (diameter 200 μm) that were insulated by parylene of a 5-μm thickness to deliver electrical stimulation to the AAC (Fig. 2A). The tips of all electrodes were tapered by electrochemical etching to minimize the lesion effects of the targeted area. The stimulation electrodes were implanted bilaterally in the ACC (AP 1.0 mm, LA ± 0.5 mm, DV -2.5 mm from the bregma) simultaneously using a specially designed electrode holder (Fig. 2B). The electrodes were then firmly secured with dental cement and the anchor.

A multi-stranded extension cable was subcutaneously implanted to connect the electrodes and stimulator. The multi-stranded wires were made with a helical structure to endure the stretching forces during the surgical operation.

Behavioral test

To measure mechanical allodynia, the rats were placed in a plastic dome and innocuous mechanical stimuli were applied with a von Frey filament (8 mN bending force) ten times (once every 3–4 s) to the sensitive area of the hind paw. The frequency of foot withdrawal, expressed as a percentage, was used as the index for mechanical allodynia. Data was taken before stimulation, at 10, 20, 30, 40, 50, and 60 min during stimulation, and 0, 10, 20, and 30 min after stimulation was terminated.

Statistical analysis

Data were expressed as mean $\pm$ S.E.M. Statistical tests were done using the one-way repeated measures analysis of variance (ANOVA) followed by the LSD as a post hoc test at each time point. Independent sample *t*-tests were used when comparisons involved only two groups. A *p*-value of less than 0.05 was considered statistically significant.

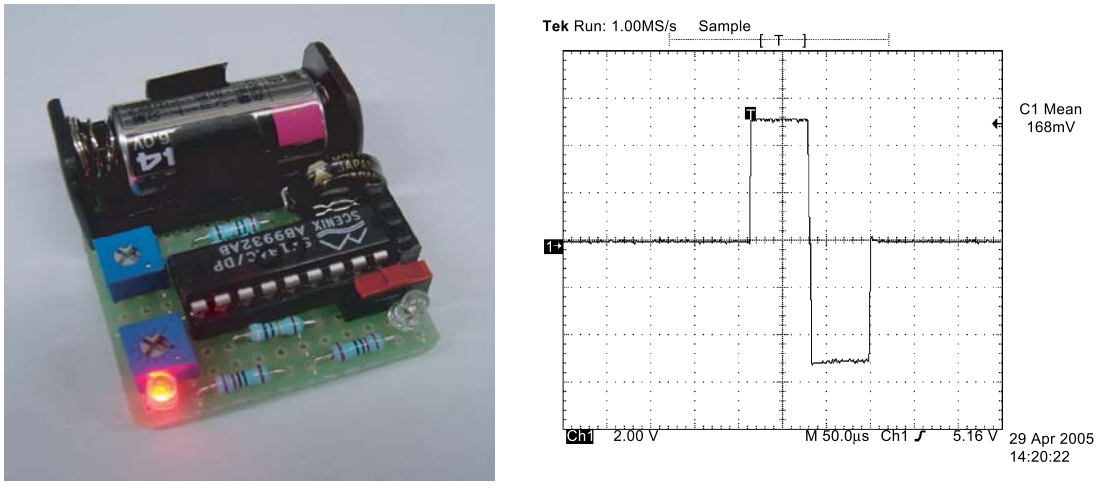

Fig. 1. (A) Portable brain stimulator; (B) biphasic output pulse of the stimulator

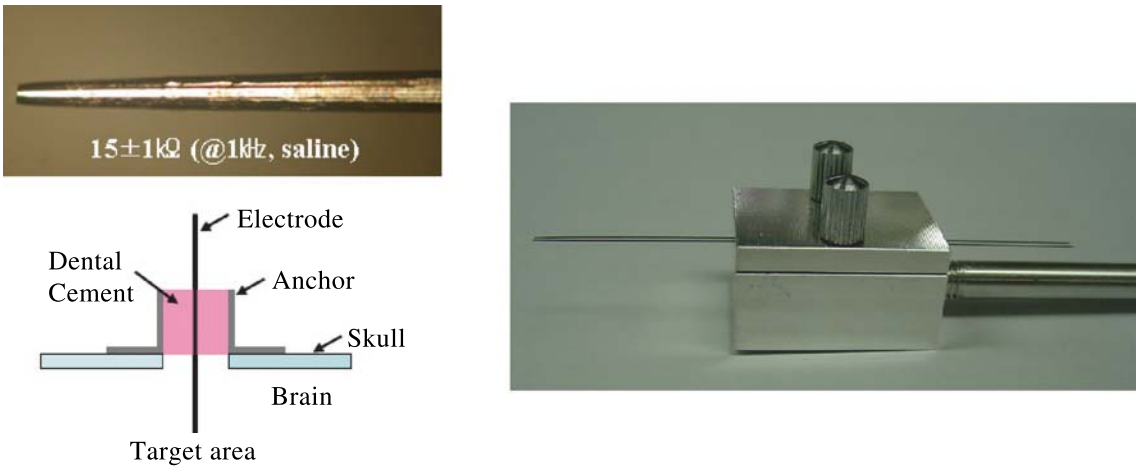

Fig. 2. (A) Stimulation electrode and electrode fixation method; (B) electrode holder for bilateral implantation

Histology

At the end of the experiment, the animals were sacrificed with an overdose of urethane (1.25 g/kg, i.p.) and perfused transcardially with normal saline followed by 4% paraformaldehyde (in 0.1 M sodium phosphate-buffered, pH 7.4). The brains were removed and stored in 30% sucrose for three days. Serial coronal sections (30 μm thickness) of the brain were stained with cresyl violet to access the anatomic localization and histological verification of the stimulating electrode track. The site of the stimulating electrodes was determined using a light microscope.

Results

The 6-channel output portable brain stimulator and the output biphasic pulse are shown in Fig. 1. The total weight of each stimulator was $19 + 1$ g including the battery, and the stimulators were positioned on the backs of the pain models with backpacks. In this study, a constant voltage stimulus, a bipolar biphasic square wave pulse with the duration of 60 μs, was delivered to the ACC through the electrodes. The intensity of the electrical stimulation was 0.6 V, and the high frequency of 130 Hz was applied for 60 min.

The stimulation electrodes, their fixation method, and the electrode holder for bilateral implantation are shown in Fig. 2. The shape of the stimulation site was a flat circle with a diameter of 100 ± 5 μm. The impedance of the stimulation electrodes was measured by electrochemical methods using a potentiostat (Zahner Elektrik IM6e, Germany), and the value was about 15 ± 1 KΩ with 1 KHz in saline. Long-term use silicone (NuSil, USA) molded into multi-stranded extension cables were created to make the electrical connection between the stimulator and electrodes. The total length and resistance of the cables were 9 cm and less than 1.0 ± 0.2 Ω, respectively.

The scene of the bilateral electrode implantation in the ACC with the holder is shown in Fig. 3A. The metal

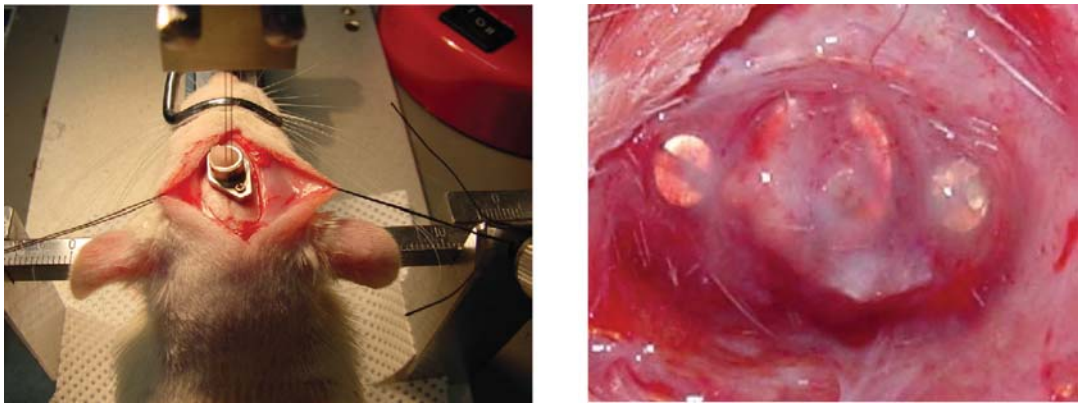

Fig. 3. The scene of bilateral electrode implantation in the ACC with the electrode holder (A and B)

anchor was fixed on the rat's skull with two screws, and its weight was about 0.9 g. After the electrode implantation, dental cement was added in the well structure of the anchor to secure the electrodes. We also verified there were no infections or inflammations six weeks after the anchor implantation. Also, we confirmed that there was no tissue damage caused by the metal anchor (Fig. 3B).

We performed cresyl violet staining to confirm the correct location of the stimulation electrodes in the ACC after the behavioral test. As shown in Fig. 4, we verified the electrodes were properly implanted in the ACC by the tracks of the electrodes.

The rats were divided into four experimental groups: a normal group ($n = 4$); a pain group ($n = 4$) with neuropathic pain; a pain ACC stimulation group ($n = 5$) subjected to electrical stimulation while the stimulation electrode was placed in the ACC with neuropathic pain; and a pain sham ACC stimulation group ($n = 4$) in which no electrical stimulation was applied while the stimulation electrode was placed in the ACC with neuropathic pain. A subject that had all the described devices implanted is shown in Fig. 5A, and all subjects were given the behavioral test with the described devices. A photograph of the behavioral test is shown in Fig. 5B.

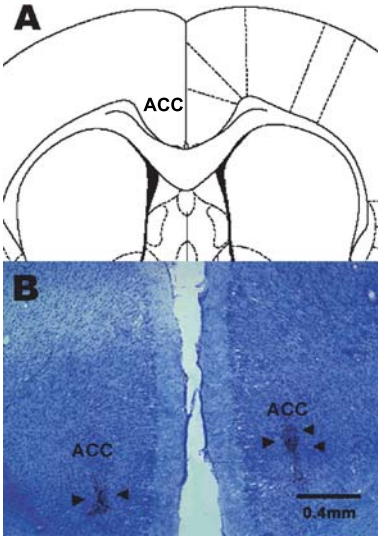

Fig. 4. (A) Histological reconstructions in the ACC and (B) photomicrograph of the stimulation site in the ACC. Triangles indicate that the bilateral stimulation electrode has entered the ACC (ACC: AP 1.0 mm, LA ±0.5 mm, DV −2.5 mm from bregma)

We measured mechanical allodynia before, after, and during electrical stimulation of the ACC. In the ACC, the electrical stimulation significantly reduced the response to pain (Fig. 6). The pain ACC stimulation group exhibited the lowest mechanical allodynia score when compared to the pain and pain sham ACC stimulation groups. The effect of the electrical stimulation of the ACC on neuropathic pain was shown during the stimulation at 30, 40, 50, and 60 min, and at 10 min after stimulation. At 50 min after the beginning of ACC electrical stimulation, the pain ACC stimulation group ($65.1 \pm 8.3\%$) showed a reduced effect of the ACC stimulation compared to the pain group ($100.0 \pm 0.0\%$) and the pain sham ACC stimulation group ($100.0 \pm 0.0\%$). The pain group and the pain sham ACC stimulation group showed similar effects. The effect of the ACC electrical stimulation was not sustained for long after the stimulator was turned off. When the time of stimulation was 60 min, the effect of the stimulation continued for 10 min. The normal, pain, and pain sham ACC stimulation groups were not affected. Particularly, the lack of change in the response of the pain sham ACC stimulation proved the effect of the ACC stimulation.

The summary of data is shown in Fig. 7. The data were separated on the basis of the beginning and termination

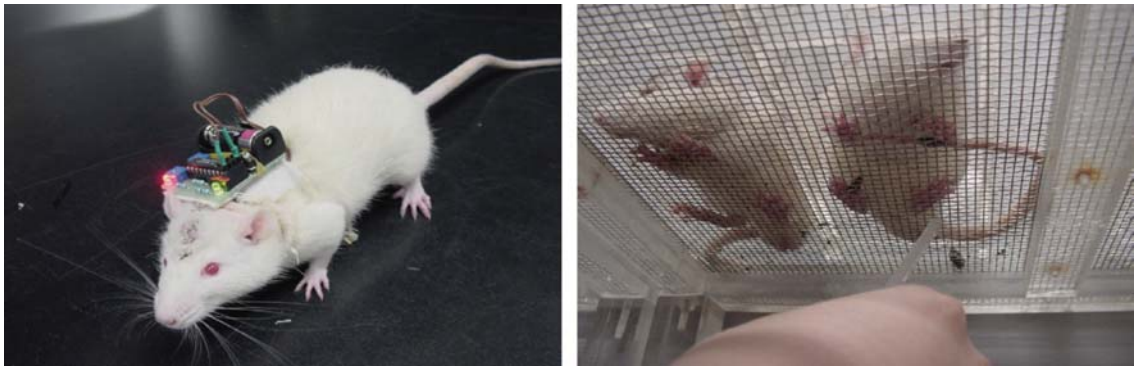

Fig. 5. (A) Neuropathic pain model that is used in the behavioral test. (B) The scene of the behavioral test

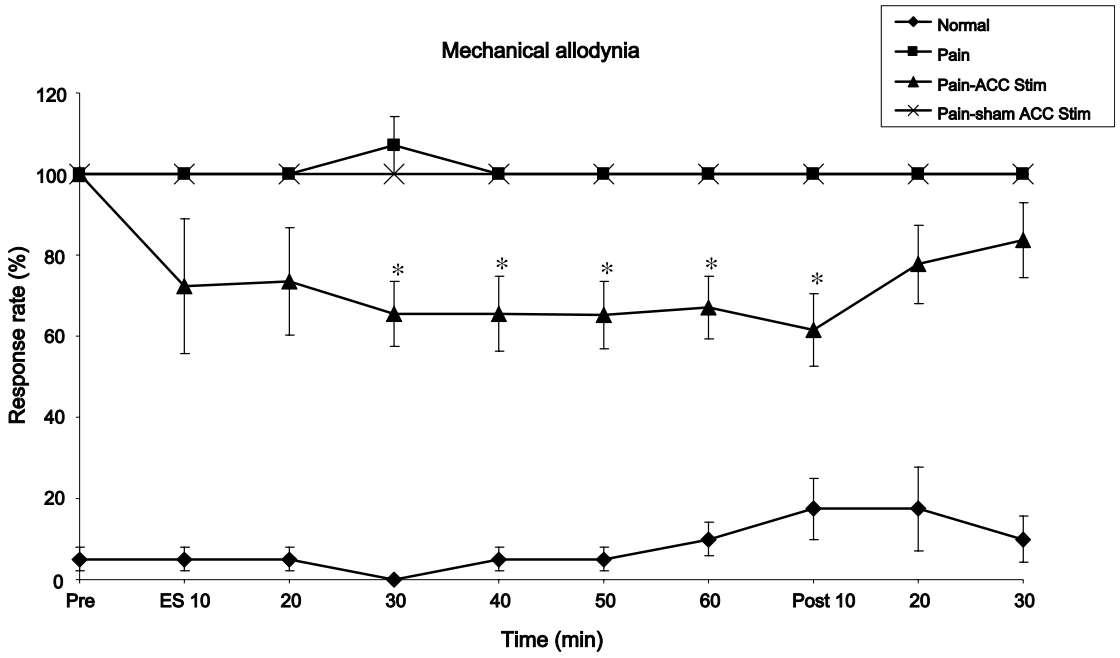

Fig. 6. Effects of the ACC electrical stimulation on mechanical allodynia. The data are expressed as mean ± S.E.M. *Denotes a *P*-value of less than 0.05, which is considered statistically significant

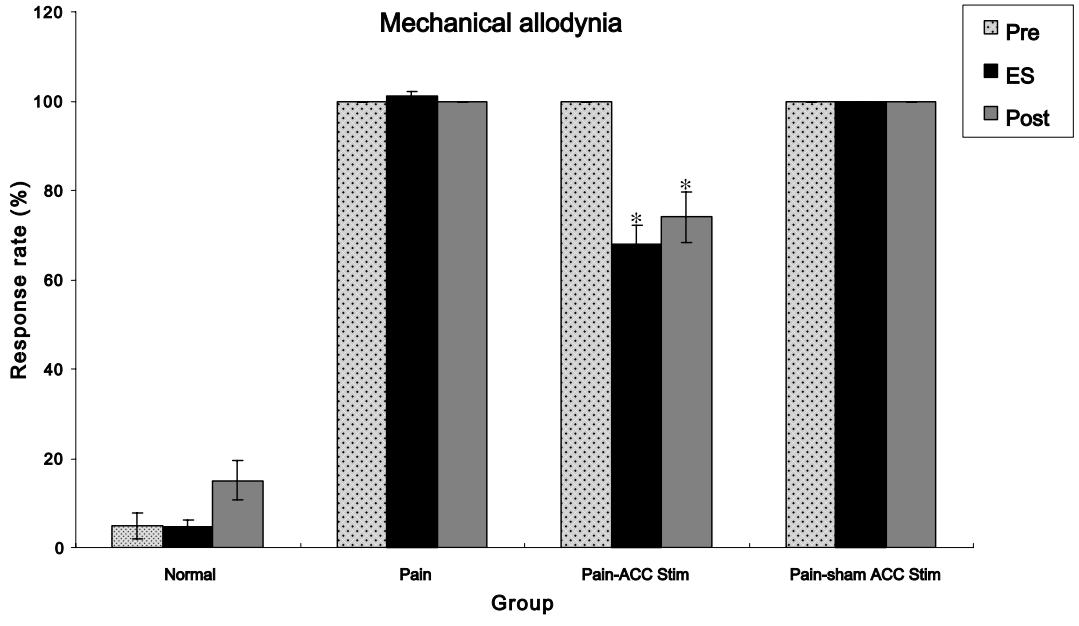

Fig. 7. Effects of the ACC stimulation on the sum for each time on mechanical allodynia. The data are expressed as mean ± S.E.M. *Denotes a *P*-value of less than 0.05, which is considered statistically significant

times of the ACC electrical stimulation. Pre-data are the sum of the responses before the electrical stimulation. ES-data are the sum of the responses during the electrical stimulation. Post-data are the sum of the responses after the electrical stimulation. In the pain ACC stimulation group, the response of the mechanical allodynia was significantly reduced during the time of ACC electrical stimulation ($68.2 \pm 4.1\%$) and after the time of ACC electrical stimulation ($74.4 \pm 5.6\%$). On the other hand, the pain and pain sham ACC electrical stimulation groups had equal responses before, during, and after the time of ACC electrical stimulation.

Discussion

In the present study, we found that bilateral electrical stimulation of the ACC is the major factor that significantly reduces the mechanical allodynia in a rat neuropathic pain model.

Neuropathic pain is caused by peripheral nerve injury or tissue damage. This pain is usually resistant to analgesic medical therapy and is extremely unpleasant. The symptoms of this pain are hyperalgesia, allodynia, spontaneous pain, crushing sensations, and deep aching. Due to the generally intractable and incapacitating nature of this pain, various studies have attempted to address pain management. These include deep brain stimulation (DBS), spinal cord stimulation, transcutaneous electrical nerve stimulation (TENS), anterior cingulotomy, and dorsal root entry zone lesions. One of these studies, the electrical brain stimulation of the ACC, has recently received considerable attention for the treatment of pain. To control neuropathic pain, there are various target positions for electrical brain stimulation, according to the various pain mechanisms.

The cingulate cortex is one of the largest parts of the limbic lobe and the limbic system. The cingulate region is subdivided into the rostal and mid-cingulate regions. The mid-cingulate region is further separated into an anterior and posterior portion [26]. The ACC is related to many pain mechanisms. A direct role of the ACC in processing nociceptive information has been proven by PET studies. These studies show that the ACC is activated during the application of acute, noxious-heat stimuli to the body surface [3, 21]. Functional imaging studies suggest that the cingulated and prefrontal cortex may respond together during responses to noxious stimuli in chronic pain syndromes. The administration of morphine to an individual suffering from chronic pain following the removal of a squamous carcinoma in the left jaw elevated blood flow in the anterior cingulate cortex as well as in the prefrontal and insular cortices [12]. The ACC is mainly reported to be the site that is activated following nociceptive stimulation in human functional imaging studies [19]. There is considerable experimental evidence from animal studies implicating the cingulate cortex in the modulation of nociception. Electrophysiological studies have shown that the ACC receives nociceptive input [4].

These results raise the question of whether the net effects of electrical brain stimulation are in fact inhibitory or excitatory. To this day, the fundamental knowledge regarding the interactions that occur between the neurons of the central nervous system and applied electrical currents has been lacking. However, a number of possible mechanisms have been proposed [6]. One of the more popular hypotheses is that electrical brain stimulation causes a reduction of neuronal activity by means of a depolarization block. This proposed mechanism involves the suppression of voltage-gated sodium and T-type calcium currents, leading to an interruption of spontaneous activity within the neurons [1]. It has also been proposed that the silencing of target nuclei by high-frequency stimulation is achieved by the stimulation of GABAnergic afferents to the target cells and the consequent hyperpolarization of postsynaptic terminals by the release of the inhibitory neurotransmitter GABA [16].

We also investigated the effect of the electrical stimulation of the ACC in other behavioral tests as well as the mechanical allodynia. In a hot plate test, we did not obtain the data similar to the result of the von Frey test. Dowdall *et al.* showed the comparison data of the different rat models of peripheral nerve injury [7]. According to this study, the animal model used in the present study [13] for neuropathic pain showed a small amount of lifting behavior on the hot plate. Because of these results, we suppose that the result of the hot plate test does not show the same effect due to electrical stimulation of the ACC as mechanical allodynia does.

Conclusion

We developed the portable electrical brain stimulator, metal anchor, and electrode holder to investigate the pain-relieving effects of ACC electrical stimulation. We showed, using a mechanical allodynia test of the rat models, that neuropathic pain could be modulated under the ACC electrical stimulation. The effect of ACC electrical stimulation did not continue for long after the stimulator was turned off. When the duration of stimulation was 60 min, the pain reduction was sustained for 10 min after the stimulation.

As a further study, we will investigate more effective parameters of stimulation and perform various pain tests to prove the pain-relieving effect more clearly.

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References

1. Beurrier C, Bioulac B, Audin J, Hammond C (2001) High-frequency stimulation produces a transient blockade of voltage-gated currents in subthalamic neurons. J Neurophysiol 85: 1351–1356
2. Calejesan AA, Kim SJ, Zhuo M (2000) Descending facilitatory modulation of a behavioral nociceptive response by stimulation in the adult rat anterior cingulate cortex. Eur J Pain 4: 83–96
3. Casey KL, Minoshima S, Berger KL, Koeppe RA, Morrow TJ, Frey KA (1994) Positron emission tomographic analysis of cerebral structures activated specifically by repetitive noxious heat stimuli. J Neurophysiol 71: 802–807
4. Davis KD, Taylor SJ, Crawley AP, Wood ML, Mikulis DJ (1997) Functional MRI of pain- and attention-related activations in the human cingulate cortex. J Neurophysiol 77: 3370–3380
5. Devinsky O, Morrell MJ, Vogt BA (1995) Contributions of anterior cingulate cortex to behaviour. Brain 118 (Pt 1): 279–306
6. Dostrovsky JO, Lozano AM (2002) Mechanisms of deep brain stimulation. Mov Disord 17 [Suppl] 3: S63–S68
7. Dowdall T, Robinson I, Meert TF (2005) Comparison of five different rat models of peripheral nerve injury. Pharmacol Biochem Behav 80: 93–108
8. Erel U, Arborelius L, Brodin E (2004) Increased cholecystokinin release in the rat anterior cingulate cortex during carrageenan-induced arthritis. Brain Res 1022: 39–46
9. Garcia-Larrea L, Peyron R, Mertens P, Gregoire MC, Lavenne F, Le Bars D, Convers P, Mauguiere F, Sindou M, Laurent B (1999) Electrical stimulation of motor cortex for pain control: a combined PET-scan and electrophysiological study. Pain 83: 259–273
10. Hsu MM, Shyu BC (1997) Electrophysiological study of the connection between medial thalamus and anterior cingulate cortex in the rat. Neuroreport 8: 2701–2707
11. Hutchison WD, Davis KD, Lozano AM, Tasker RR, Dostrovsky JO (1999) Pain-related neurons in the human cingulate cortex. Nat Neurosci 2: 403–405
12. Jones AK, Friston KJ, Qi LY, Harris M, Cunningham VJ, Jones T, Feinman C, Frackowiak RS (1991) Sites of action of morphine in the brain. Lancet 338: 825
13. Lee BH, Won R, Baik EJ, Lee SH, Moon CH (2000) An animal model of neuropathic pain employing injury to the sciatic nerve branches. Neuroreport 11: 657–661
14. Lei LG, Sun S, Gao YJ, Zhao ZQ, Zhang YQ (2004) NMDA receptors in the anterior cingulate cortex mediate pain-related aversion. Exp Neurol 189: 413–421
15. Meyerson BA, Lindblom U, Linderoth B, Lind G, Herregodts P (1993) Motor cortex stimulation as treatment of trigeminal neuropathic pain. Acta Neurochir [Suppl] 58: 150–153
16. Moser A, Gieselberg A, Ro B, Keller C, Qadri F (2003) Deep brain stimulation: response to neuronal high frequency stimulation is mediated through GABA(A) receptor activation in rats. Neurosci Lett 341: 57–60
17. Ortega-Legaspi JM, Lopez-Avila A, Coffeen U, del Angel R, Pellicer F (2003) Scopolamine into the anterior cingulate cortex diminishes nociception in a neuropathic pain model in the rat: an interruption of 'nociception-related memory acquisition'? Eur J Pain 7: 425–429
18. Peyron R, Garcia-Larrea L, Deiber MP, Cinotti L, Convers P, Sindou M, Mauguiere F, Laurent B (1995) Electrical stimulation of precentral cortical area in the treatment of central pain: electrophysiological and PET study. Pain 62: 275–286
19. Peyron R, Laurent B, Garcia-Larrea L (2000) Functional imaging of brain responses to pain. A review and meta-analysis (2000). Neurophysiol Clin 30: 263–288
20. Rushton DN (2002) Electrical stimulation in the treatment of pain. Disabil Rehab 24: 407–415
21. Talbot JD, Marrett S, Evans AC, Meyer E, Bushnell MC, Duncan GH (1991) Multiple representations of pain in human cerebral cortex. Science 251: 1355–1358
22. Tasker RR, Vilela Filho O (1995) Deep brain stimulation for neuropathic pain. Stereotact Funct Neurosurg 65: 122–124
23. Treede RD, Kenshalo DR, Gracely RH, Jones AK (1999) The cortical representation of pain. Pain 79: 105–111
24. Tsubokawa T, Katayama Y, Yamamoto T, Hirayama T, Koyama S (1991) Chronic motor cortex stimulation for the treatment of central pain. Acta Neurochir [Suppl] 52: 137–139
25. Velisek L, Veliskova J, Moshe SL (2002) Electrical stimulation of substantia nigra pars reticulata is anticonvulsant in adult and young male rats. Exp Neurol 173: 145–152
26. Vogt BA, Berger GR, Derbyshire SW (2003) Structural and functional dichotomy of human midcingulate cortex. Eur J Neurosci 18: 3134–3144

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Long term follow-up results of dorsal root entry zone lesions for intractable pain after brachial plexus avulsion injuries

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Summary

Brachial plexus avulsion injury is one of the major complications after traffic, especially motorcycle accidents and machine injuries. Intractable pain and paralysis of the affected limbs are the major neurological deficits. During the past 18 years, we have encountered and treated more than 500 cases with brachial plexus avulsion injuries. Dorsal root entry zone lesions (DREZ) made by thermocoagulation were performed for intractable pain in 60 cases. Forty cases were under regular follow-up for 5–18 years. In early postoperative stage, the pain relief rate was excellent or good in 32 cases (80%). The pain relief rate dropped to 60% in 5 year follow-up period and only 9 cases (50%) had excellent or good result in 10 year follow-up. Reconstructive procedures were performed in almost all patients in the last 10 years. Dorsal root entry zone lesion is an effective procedure for pain control after brachial plexus avulsion injuries.

Keywords: Brachial plexus avulsion injury; dorsal root entry zone; neural reconstruction.

Introduction

Brachial plexus avulsion injury is one of the major complications after traffic, especially motorcycle accidents and machine injuries [2–5]. Motorcycles are the main transportation vehicle in many developing countries. Intractable pain after root avulsion and paralysis in the affected limbs are the consequences of brachial plexus injury. Since the majority of patients are young and middle aged people, the disability due to pain and paralysis does usually result in limitation of social activities and employment [3–5, 9].

Pain occurs frequently after injury, starting usually within weeks of the event and then, becomes chronic. The pain is almost unresponsive to medication, including narcotics and anticonvulsants [2, 6, 7]. Surgical treatment including dorsal root entry zone lesion (DREZ) has been used for control of pain [6–9]. For brachial plexus avulsion injury, neurosurgeons, plastic surgeons, and orthopedic doctors cooperate in trying to relieve the pain and restore the function of the affected limbs [1, 4, 5]. In the past 18 years, we have encountered more than 500 patients with brachial plexus injury. Dorsal root entry zone lesions were used for pain control.

Material and method

Since 1987, we have treated more than 500 cases with brachial plexus injuries. The main complaints were intractable pain and paralysis of the affected limbs. Injuries were evaluated by physical examination, electrodiagnostic studies and imaging studies including myelography in early years, thereafter magnetic resonance imaging in the last 15 years (Fig. 1) [1, 4, 5, 9].

Sixty patients underwent DREZ lesions with radiofrequency thermocoagulation for pain control. Among these 60 cases, 40 cases had 5–18 year follow-up [9, 10]. There were 36 male and 4 female patients. Age distribution was from 25 to 71 years with a mean age of 49.5 years. The intervals between injury and surgery varied from 0.5 to 25 years with a mean of 8.5 years. Seventeen cases had injuries on the right. Thirty-two cases suffered from complete brachial plexus avulsion injuries; 5 cases with upper brachial plexus injuries and 3 with lower brachial plexus injuries. All patients were found to have poor response to medical treatment and underwent DREZ lesions. DREZ surgery might be performed before or after nerve reconstruction. The surgical principles were performed following Nashold method [8] with some modification. Hemilaminectomy regions depended on the avulsed roots. For a complete brachial plexus avulsion injury, hemilaminectomy from C4 to T1 was performed to expose the whole lesion site. The electrode had an internal thermistor to measure the temperature of lesion site and was introduced into the cord along the posterior lateral sulcus into the dorsal horn of the cord. Each lesion was made at a temperature of 75 °C for 15 to 20 (in the C5–6 cord) seconds (Fig. 2). The interval between two lesions was about 1–2 mm.

Most patients in the last 10 years underwent different kinds of reconstructive procedures for brachial plexus injuries. The procedures were performed depending on the condition of injuries and might be before or after DREZ surgery for pain control [4, 5].

Almost all patients were under regular follow-up for adjuvant procedures or adjustment of medication. These could help patients for a better quality of life.

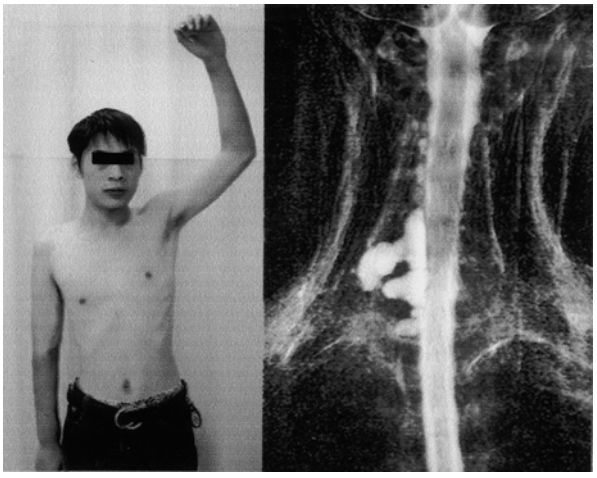

Fig. 1. A case suffered from right brachial plexus avulsion injury and complete paralysis in the right upper limb. MRI showed traumatic meningoceles in cervical and upper thoracic spine

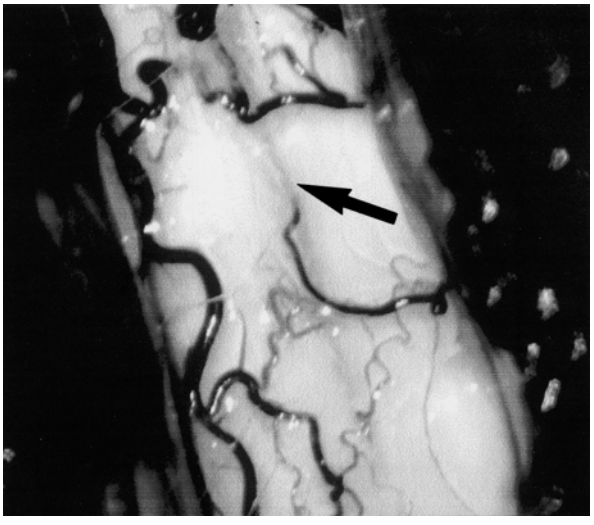

Fig. 2. All dorsal roots were torn (arrow)

Results

In the initial stage, thirty-two patients (80%) had excellent-good pain control after DREZ surgery. Five patients had only fair results and three complained of no improvement. After 3 years' follow-up, the excellent-good pain control group dropped to 75% (30 cases). There were 38 patients with 5 year follow-up and 23 patients (60%) still had excellent-good results. The patients needed narcotics for pain control and five patients complained of return of original pain despite medication. After a 10 year follow-up, 9 cases (50%) had at least good result and 5 cases needed narcotic pain control (Table 1).

Table 1. *Long term follow-up of pain relief rate after DREZ surgery*

Result \ Follow-up	Early stage	3 year follow-up	5 year follow-up	10 year follow-up
Excellent–good	32 (80%)	30 (75%)	23 (60%)	9 (50%)
Fair	5 (12.5%)	5 (12.5%)	10 (27%)	5 (28%)
No improvement	3 (7.5%)	5 (12.5%)	5 (13%)	4 (22%)

Excellent Nearly no medication for pain, *good* analgesics were needed sometimes, *Fair* narcotics were needed, *no improvement* original pain persisted.

Two patients underwent stereotactic thalamotomy 2 and 3 years after DREZ surgery due to recurrence of pain. One showed good postoperative result.

Discussion

The clinical manifestations after brachial plexus avulsion injury are mainly intractable pain and paralysis of the affected limb. The goal of treatment is early return to social activities or even work [4, 5, 10]. The deafferentation pain after root avulsion is very incapacitating.

There were five patients in our series that committed suicide and half of patients had thought about suicide [4]. In our experience, pain may happen in about one third of patients. Good pain control is treatment priority.

For pain control, our experience suggests that DREZ can be performed as early as possible. There were no major postoperative complications encountered in our 60 cases. Temporary ataxic gait might be found in about 15 cases (25%). This symptom usually improved gradually to near normal gait within 3 months [4]. Although opinions differ regarding the timing of DREZ surgery, most authors recommended surgery within 3 to 6 months of injury. Most patients in our series underwent exploration later than this period. This is due to patients' hesitation or inadequate information. Five patients underwent above elbow amputation before DREZ surgery. Unfortunately, phantom limb pain developed. We do not recommend this surgical procedure in those patients.

Though pain relief rate after DREZ surgery decreased year by year, it is still a treatment choice for intractable pain after brachial plexus avulsion injury. Good pain control definitely gives patients much benefit in social activities and employment.

References

1. Alon M, Rochkind S (2002) Pre-, intra, and postoperative electrophysiologic analysis of the recovery of old injuries of the peripheral nerve and brachial plexus after microsurgical management. J Reconstr Microsurg 18: 77–82
2. Carvalho GA, Nikkhah G, Samii M (1997) Pain management after post-traumatic brachial plexus lesions, conservative and surgical therapy possibilities. Orthopode 26(7): 621–625

3. Chen HJ (1992) Dorsal root entry zone lesions in the treatment of pain following brachial plexus avulsion and herpes zoster. J Formos Med Assoc 91: 508–512
4. Chen HJ, Lu k, Yeh MC (2003) Combined dorsal root entry zone lesions and neural reconstruction for early rehabilitation of brachial plexus avulsion injury. Acta Neurochir [Suppl] 87: 95–97
5. Chuang DC (1995) Neurotization procedures for brachial plexus injuries. Hand Clin 11(4): 633–645
6. Ishijima B, Shimoji K, Simizu H (1988) Lesions of spinal and trigeminal dorsal root entry zone for deafferentation pain: experience of 35 cases. Apply Neurophysiol 51: 175–187
7. Mertens P, Sindou M (2000) Surgery in the dorsal root entry zone for treatment of chronic pain. Neurochirurgie 46: 429–446
8. Nashold BS Jr (1988) Neurosurgical technique of the dorsal root entry zone operation. Apply Neurophysiol 51: 136–145
9. Samii M, Bear-Henney S, Ludemann W, Tatagiba M, Blomer U (2001) Treatment of refractory pain after brachial plexus avulsion with dorsal root entry zone lesion. Neurosurgery 48: 1269–1275
10. Sindou M (1995) Microsurgical DREZotomy for pain, spasticity and hyperactive bladder: a 20-year experience. Acta Neurochir (Wien) 137: 1–5

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Endogenous and exogenous modulators of potentials evoked by a painful cutaneous laser (LEPs)

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Summary

Little is known about the specific functions of the human cortical structures receiving nociceptive input, their relationship to various dimensions of pain, and the modulation of these inputs by attention. We now review studies demonstrating the subdural potentials evoked by a cutaneous laser stimulus which produces a pure pain sensation by selective activation of cutaneous nociceptors (LEPs). These LEPs were localized over human anterior and middle cingulate (A & MCC), somatosensory (SI) and parasylvian (PS) cortices. LEP, lesion and imaging data define pain-related elements within each of these structures: insula and parietal operculum within PS, anterior and middle cingulate cortex, and possibly Brodman's areas 3a, 3b and 1 within SI. LEPs recorded over each of these areas is modulated with laser intensity and evoked pain. Attention to the painful laser produces an increase in the amplitude of LEPs over all three cortical areas and emergence of a late positive potential over ACC alone. These studies provide clear evidence of human cortical structures receiving nociceptive input and the modulation of that input by exogenous (e.g. laser intensity) and endogenous factors (e.g. directed attention).

Keywords: Human pain; ventral posterior thalamus; anterior cingulated; primary somatic sensory cortex; secondary somatic sensory cortex; insula; parietal operculum.

Cortical pain mechanisms have been mysterious since Penfield pointed out the sensation of pain was (almost) never evoked by cortical stimulation [35]. Imaging studies have demonstrated three primary areas activated by painful stimuli: the primary sensory cortex (SI), the parasylvian cortex (PS), and the middle cingulate cortex (MF) [40, 13]. We have demonstrated that cutaneous application of a cutaneous (painful) laser simultaneously evokes LEPs from the cortical surface of the anterior and middle cingulate, PS, and SI cortex [32].

In PS, the presence of generators is demonstrated by local polarity reversals [26, 32, 43]. In SI, the lack of polarity reversal and the presence of potentials on either side of the central sulcus suggest that there is a deep or tangential generator in SI, perhaps in BA 3a or 3b, or the 3b-1 junction [32], which is medial to the generator of the vSEP in BA3b [32, 39]. These SI LEP results may be consistent with evidence of nociceptive stimuli which activate area 3a deep in the central sulcus [11, 42] and/or of area 1 [38] or at the border between areas 1 and 3b [22].

LEPs recorded on the subdural surface of the ACC, were greater on the contralateral than the ipsilateral side [27, 41]. These results also demonstrate that LEP P2s can be recorded over perigenual ACC, perhaps consistent with pain sensory- or attention-related activation of mid- to perigenual ACC [14, 16]. The rapid fall-off in amplitude and polarity reversal for electrodes around the cingulate sulcus (CiS) demonstrates that these potentials arise in the CiS.

Source analysis of PS LEP generator is most consistent with a LEP generator on the deep surface of the parietal operculum at the junction with insula [43].

This data shows somatotopy with hand (posterior) and face (anterior) [4] cf. [19] perpendicular to the mediolateral somatotopy reported for SII [11, 24]. Our lesion data [20] and numerous imaging studies suggest that there are at least two PS generators (parietal operculum and insula) [5, 8, 9, 10, 36].

Laser stimuli of graded intensity were used to demonstrate that LEPs (N2 and P2) were correlated with energy and with pain ratings of laser pulses in all three areas, except the N2 potential recorded over PS [33]. These results suggest that all three areas, and the different functions that they serve, involve input arising from nociceptors which are modulated with laser energy.

The separate and distinct loss of function produced by discrete lesions of different structures in the forebrain

is the basis of localization in clinical neurology [1]. Lesions of SI lead to impaired discrimination of temperature in the painful range [23, 37]. Psychophysical evaluation of six patients with PS lesions demonstrated that patients with impaired discrimination of experimental pain (i.e., elevated pain thresholds) shared lesions of the posterior parietal operculum and the most posterior part of the insula [20] operculum, showed normal thresholds. Patients with lesions of the insula, regardless of opercular involvement, demonstrated an increased tolerance for pain [20].

Other studies in patients with insular lesions have demonstrated an increased tolerance for pain [2] see also [17, 29]. The interpretation of this increased pain tolerance may be as a function of motivation [3], attention/distraction [12, 21, 30] cf. [18], affect [7], and/or cognitive variables [15]. Therefore, these discrete lesions each produced a different and separate loss of function.

Recent studies have examined changes in LEPs produced by attention to or distraction from the painful laser. During the attention task patients counted the number of painful stimuli. During the distraction task the patients read a passage with the expectation of answering questions testing their comprehension of the passage. Attention directed to the laser stimulus produces a highly significant increase in LEP amplitude (N2 and P2) in SI, PS, and ACC, and emergence of a late positive component (350 ms – LP) over the caudal ACC and BA6 [28, 34]. Additionally, the attention evoked by novel stimuli (oddball paradigm) [25] led to a late positive potential (P300), unlike the P2 or LP, over the medial temporal lobe, and perhaps a source for attention evoked by novelty.

We examined attention evoked by infrequent events. The oddball paradigm consists of random infrequent stimuli (e.g. low frequency tones) in a series of frequent events (e.g. high frequency tones), and is a well established technique for evoking the P300, a potential evoked by attended, infrequent events. Our data demonstrates that the morphology, latency and subdural location of LEPs were biphasic, onset 200 ms parietal operculum – very different from those of the auditory P300 [25]. This is confirmed by source analysis of LEP generators which indicate that the LEP generator is located between the parietal operculum and the insula about 1 cm anterior and superior to the AEP NI generator in Heschl's convolutions [6].

These results demonstrate our ability to study directed attention and novelty (oddball paradigm) with subdural electrodes during seizure monitoring. Therefore, increased ERD is associated with directed attention and increases in pain due to increased laser power, attention or endogenous factors.

Cortical activation can be signaled by changes in the ongoing cortical rhythms, known as event related desynchronization (ERD). Studies based on subdural EEG recordings from electrodes on the brain (ECoG), demonstrate the intracranial structures generating pain-related ERD which is dependent upon attention to painful stimuli [31]. Pain-related subdural (ECoG) activation was present over SI, PS and ACC during attention but decreased over PS during distraction. ERD was consistently decreased over PS when the pain intensity was decreased due to decreased laser energy, to distraction, or even during an apparently endogenous, spontaneous increase in pain intensity during the distraction condition. These studies provide clear evidence of human cortical structures receiving nociceptive input and the modulation of that input by exogenous (e.g. laser intensity) and endogenous (directed attention) factors.

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References

1. Adams RD, Victor M, Ropper AH (1996) Principles of neurology. McGraw-Hill, New York
2. Berthier M, Starkstein S, Leiguarda R (1988) Asymbolia for pain: a sensory-limbic disconnection syndrome. Ann Neurol 24: 41–49
3. Blitz B, Dinnerstein AJ (1968) Effects of different types of instructions on pain parameters. J Abnorm Psychol 73: 276–280
4. Blomqvist A, Zhang ET, Craig AD (2000) Cytoarchitectonic and immunohistochemical characterization of a specific pain and temperature relay, the posterior portion of the ventral medial nucleus, in the human thalamus. Brain 123 Pt 3: 601–619
5. Casey KL, Minoshima S, Berger KL, Koeppe RA, Morrow TJ, Frey KA (1994) Positron emission tomographic analysis of cerebral structures activated specifically by repetitive noxious heat stimuli. J Neurophysiol 71: 802–807
6. Celesia GG, Puletti F (1969) Auditory cortical areas in man. Neurology 19: 211–220
7. Chen AC, Dworkin SF, Haug J, Gehrig J (1989) Human pain responsivity in a tonic pain model: psychological determinants. Pain 37: 143–160
8. Coghill RC, Gilron I, Iadarola MJ (2001) Hemispheric lateralization of somatosensory processing. J Neurophysiol 85: 2602–2612
9. Coghill RC, Sang CN, Maisog JM, Iadarola MJ (1999) Pain intensity processing within the human brain: a bilateral, distributed mechanism. J Neurophysiol 82: 1934–1943
10. Coghill RC, Talbot JD, Evans AC, Meyer E, Gjedde A, Bushnell MC, Duncan GH (1994) Distributed processing of pain and vibration by the human brain. J Neurosci 14: 4095–4108

11. Craig AD (1995) Supraspinal projections of lamina one neurons. In: Besson JM, Guilbaud G, Ollat H (eds) Forebrain areas involved in pain processing. Libby, London, pp 13–25
12. Crawford HJ, Knebel T, Vendemia JMC (1998) The nature of hypnotic analgesia: neurophysiological foundation and evidence. Contemporary hypnosis 15: 22–33
13. Davis KD (2000) Studies of pain using functional magnetic resonance imaging. In: Casey KL, Bushnell MC (eds) Pain Imaging. IASP Press, Seattle, pp 195–210
14. Davis KD, Taylor SJ, Crawley AP, Wood ML, Mikulis DJ (1997) Functional MRI of pain- and attention related activation in the human cingulate cortex. J Neurophysiol 77: 3370–3380
15. de Wied M, Verbaten MN (2001) Affective pictures processing, attention, and pain tolerance. Pain 90: 163–172
16. Derbyshire SWG, Vogt BA, Jones AKP (1998) Pain and stroop interference tasks activate separate processing modules in anterior cingulate cortex. Exp Brain Res 118: 52–60
17. Dong WK, Hayashi T, Roberts VJ, Fusco BM, Chudler EH (1996) Behavioral outcome of posterior parietal cortex injury in the monkey. Pain 64: 579–587
18. Friederich M, Trippe RH, Ozcan M, Weiss T, Hecht H, Miltner WH (2001) Laser-evoked potentials to noxious stimulation during hypnotic analgesia and distraction of attention suggest different brain mechanisms of pain control. Psychophysiology 38: 768–776
19. Graziano A, Jones EG (2004) Widespread thalamic terminations of fibers arising in the superficial medullary dorsal horn of monkeys and their relation to calbindin immunoreactivity. J Neurosci 24: 248–256
20. Greenspan JD, Lee RR, Lenz FA (1999) Pain sensitivity alterations as a function of lesion location in the parasylvian cortex. Pain 81: 273–282
21. Hodes RL, Howland EW, Lightfoot N, Cleeland CS (1990) The effects of distraction on responses to cold pressor pain. Pain 41: 109–114
22. Kenshalo DR Jr, Isensee O (1983) Responses of primate SI cortical neurons to noxious stimuli. J Neurophysiol 50: 1479–1496
23. Kenshalo DR, Thomas DA, Dubner R (1991) Primary somatosensory cortical lesions reduce the monkeys' ability to discriminate and detect noxious thermal stimulation. Society For Neuroscience Abstract 17: 1206 (Ref type: abstract)
24. Krubitzer L, Clarey J, Tweedale R, Elston G, Calford M (1995) A redefinition of somatosensory areas in the lateral sulcus of macaque monkeys. J Neurosci 15: 3821–3839
25. Lenz FA, Krauss G, Treede RD, Lee JL, Boatman D, Crone N, Minahan R, Port J, Rios M (2000) Different generators in human temporal-parasylvian cortex account for subdural laser-evoked potentials, auditory-evoked potentials, and event-related potentials. Neurosci Lett 279: 153–156
26. Lenz FA, Rios M, Chau D, Krauss GL, Zirh TA, Lesser RP (1998a) Painful stimuli evoke potentials recorded from the parasylvian cortex in humans. J Neurophysiol 80: 2077–2088
27. Lenz FA, Rios MR, Zirh TA, Krauss G, Lesser RP (1998b) Painful stimuli evoke potentials recorded over the human anterior cingulate gyrus. J Neurophysiol 79: 2231–2234
28. Lenz FA, Treede RD (2002) Attention, novelty, and pain. Pain 99: 1–3
29. Lynch SA (1980) The functional organization of posterior parietal association cortex. Behav Brain Sci 3: 485–534
30. McCaul KD, Malott JM (1984) Distraction and coping with pain. Psychol Bull 95: 516–533
31. Ohara S, Crone NE, Weiss N, Lenz FA (2004a) Attention to pain modulates electrocorticographic event-related desynchronization during cutaneous laser stimulation in humans. Clin Neurophysiol 115: 1641–1652
32. Ohara S, Crone NE, Weiss N, Treede RD, Lenz FA (2004b) Cutaneous painful laser stimuli evoke responses recorded directly from primary somatosensory cortex in awake humans. J Neurophysiol 91: 2734–2746
33. Ohara S, Crone NE, Weiss N, Treede R-D, Lenz FA (2004c) Amplitudes of laser evoked potential recorded from primary somatosensory, parasylvian and medial frontal cortex are graded with stimulus intensity. Pain 110: 318–328
34. Ohara S, Crone NE, Weiss N, Vogel H, Treede RD, Lenz FA (2004d) Attention to pain is processed at multiple cortical sites in man. Exp Brain Res 156: 513–517
35. Penfield W, Jasper H (1954) Epilepsy and the functional anatomy of the human brain. Little Brown, Boston
36. Peyron R, Laurent B, Garcia-Larrea L (2000) Functional imaging of brain responses to pain. A review and meta-analysis (2000). Neurophysiol Clin 30: 263–288
37. Ploner M, Freund H-J, Schnitzler A (1999) Pain affect without pain sensation in a patient with a postcentral lesion. Pain 81: 211–214
38. Ploner M, Schmitz F, Freund HJ, Schnitzler A (1999) Parallel activation of primary and secondary somatosensory cortices in human pain processing. J Neurophysiol 81: 3100–3104
39. Ploner M, Schmitz F, Freund HJ, Schnitzler A (2000) Differential organization of touch and pain in human primary somatosensory cortex. J Neurophysiol 83: 1770–1776
40. Rainville P, Bushnell MC, Duncan GH (2000) PET studies of the subjective experience of pain. In: Casey KL, Bushnell MC (eds) Pain imaging. IASP Press, Seattle, pp 123–156
41. Rios M, Treede R, Lee J, Lenz FA (1999) Direct evidence of nociceptive input to human anterior cingulate gyrus and parasylvian cortex. Curr Rev Pain 3: 256–264
42. Tommerdahl M, Delemos KA, Favorov OV, Metz CB, Vierck CJ Jr, Whitsel BL (1998) Response of anterior parietal cortex to different modes of same-site skin stimulation. J Neurophysiol 80: 3272–3283
43. Vogel H, Port JD, Lenz FA, Solaiyappan M, Krauss G, Treede RD (2003) Dipole source analysis of laser-evoked subdural potentials recorded from parasylvian cortex in humans. J Neurophysiol 89: 3051–3060

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Long term results from percutaneous radiofrequency neurotomy on posterior primary ramus in patients with chronic low back pain

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Summary

Purpose. We report on our experience of percutaneous radiofrequency neurotomy (PRN) on the posterior primary ramus (PPR) with at least two years follow-up.

Methods. 228 patients underwent PRN on the PPR for refractory low back pain. 128 patients met the inclusion criteria of facetal originated pain (group II), while 100 patients did not (group I). Radiofrequency (RF) procedures were applied in the usual manner. Pain relief was assessed at 1 week, 1 month, 6 months and 2 years using visual analog scale (VAS).

Findings. Positive responders were 56% at 1 week, 46% at 1 month, 18% at 6 months, and 13% at 2 years after PRN in group I, and 78.9% at 1 week, 75.4% at 1 month, 62.5% at 6 months, and 54.7% at 2 years in group II. Prominent local tenderness, percussion tenderness, pain on getting up, extension and transitional movement, radiating pain on buttock and/or posterior thigh, and good immediate response were found to be significantly related to good outcome.

Conclusion. PRN on the PPR has long-term beneficial effects. Long-term good results can be achieved after proper selection of patients with facet joint related low back pain.

Keywords: Low back pain; percutaneous radiofrequency neurotomy (PRN); posterior primary ramus (PPR); facet joint.

Introduction

The posterior facet joints of the lumbar spine, which are innervated by the medial branch of PPR, have long been considered responsible for mechanical low back pain. The estimated prevalence of lumbar facet joint pain among patients with low back pain ranges from 15 to 40% [2, 3]. Neural block procedure and PRN on PPR had been developed as a treatment option for chronic low back pain some 20 years ago. Although this procedure is known to have short term effects on pain relief and functional disability, clinical analyses with regard to long term effects on the prognostic factors have not been performed.

Main object of this study was to evaluate the long term effect of PRN in the treatment of chronic low back pain. For that purpose, we classified patients with chronic low back pain into 2 groups: whether patients showed objective symptoms and signs originating from spinal facet joint or not. Clinical prognostic factors were evaluated and therapeutic standards suggested.

Materials and methods

We analysed patients with chronic low back pain treated with PRN on PPR between March 1997 and February 2000. Of these patients, 228 were followed up and investigated over 2 years. Inclusion criteria for the study comprised that patients had 1) preoperative low back pain with or without leg or radiating pain over 6 months' duration, 2) no meaningful neurological deficits, 3) no significant nerve root or cord compression signs or instabilities, 4) no substantial benefit from intense physical therapy for 4–6 weeks, and 5) more than 50% pain relief from diagnostic nerve block. We classified patients into group I ($n = 100$, patients did not show objective symptoms and signs [such as local paravertebral tenderness, local paravertebral percussion tenderness, and pseudoradicular pain aggravated by extension, sign of "4", and sign of reversed "4"] of facetal originated low back pain) and group II patients ($n = 128$, patients showed objective symptoms and sign of facetal originated low back pain). Exclusion criteria for the study were that patients had 1) history of industrial accident, traffic accident, and litigational problems, 2) bleeding tendency, 3) uncontrolled hypertension, and 4) systemic infection. Baseline characteristics of patients are presented in Table 1.

Surgical treatment

With the guide of a C-arm radiographic image intensifier, the level of the procedure was verified with patient in prone position. Thereafter, radiofrequency needle (SMK-C10, 22-gauge, 100 mm long, 5 mm active tip) was inserted maintaining an angle of about 10–15 degrees between needle and horizontal plane, and advanced to the point encountered at superior articular process and transverse process (Burton's point). The tip was then redirected in a slightly more cephalad and lateral direction

Table 1. *Baseline characteristics of patients*

Characteristics	Group I ($n = 100$)	Group II ($n = 128$)
Age (mean, years)	42–69 (54)	47–72 (59)
Male no. (male:female)	64 (1:0.56)	69 (1: 0.86)
Preoperative pain duration (mean, months)	6–60 (12.2)	6–33 (14.7)
Previous lumbar op./instrumentation (%)	23/5 (23/5)	28/6 (21.9/4.7)
Minimal follow up (months)	24	24

until contact with bone was lost. Because of the innervation of the facet joint from at least two spinal levels, PPR nerve block was performed at three levels for each joint. For example, if the facet joint the 5th lumbar vertebra was considered a cause of low back pain, PRN was performed at facet joints of 4th, 5th lumbar and 1st sacral vertebra [1] (Fig. 1). After establishing the site for the lesion by C-arm image intensifier, the radiofrequency probe was readjusted by electrical resistance of tissue (if radiofrequency probe was positioned within 2 mm distance from PPR, electrical resistance indicator showing 500–700 Ω) and the thresholds of sensory and motor responses from electrical stimulation (50 and 2 Hz, respectively). If sensory stimulation was noted to be between 0.2 and 1 V as deep heating sensation or paresthesia over the respective dermatome, and motor stimulation was noted to be at least 1.5 fold greater than the sensory stimulation threshold as muscle contractions in the multifidus muscle, the electrodes were judged to be at the correct site. Once the position of the electrode was satisfactory, RF treatment was performed at 80 °C for 60 seconds using RF lesion generator.

Clinical and statistical analysis

Patient's pain was evaluated by using the visual analogue scale (VAS). Patients who felt pain relief of more than 50% VAS were judged as positive responder. All patients were followed up at postoperative 1 week, 1 month, 6 months, and 24 months, and pain relief was evaluated using VAS. Then we calculated the percentage of positive responder.

Results

No patients needed further pain medication. Mean operation time was 22 minutes in the case of unilateral procedure and 34 minutes in bilateral procedure. Percentage of positive responders were 56% at 1 week, 46% at 1 month, 18% at 6 months, and 13% at 2 years after PRN in group I, and 78.9% at 1 week, 75.4% at 1 month, 62.5% at 6 months, and 54.7% at 2 years in group II. The percentage of positive responder was higher and more sustained in group II than in group I. These long term results between the 2 groups show statistically significant difference ($p < 0.05$).

Among the clinical factors facet irritation signs (prominent local tenderness, percussion tenderness, pain on getting up and extension movement, pseudoradicular pain aggravated by sign of "4", $p = 0.001$) and good immediate response ($p = 0.01$) were found to be significantly related to outcome. Age, sex, symptom duration, bilateral symptoms, favorable imaging study results, previous lumbar surgery, and degree of pain relief from diagnostic block were not.

There were no complications related to deafferentiation pain, except for only 2 patients in group I who experienced dysesthesia for 3 months after PRN. Also there were no neurological complications, but 68 patients (29.8%) experienced temporary irritating feeling on the back after PRN for 2–7 days.

Discussion

The first clinical application of RF lesion in spinal pain was introduced by Shealy in 1975 when he used

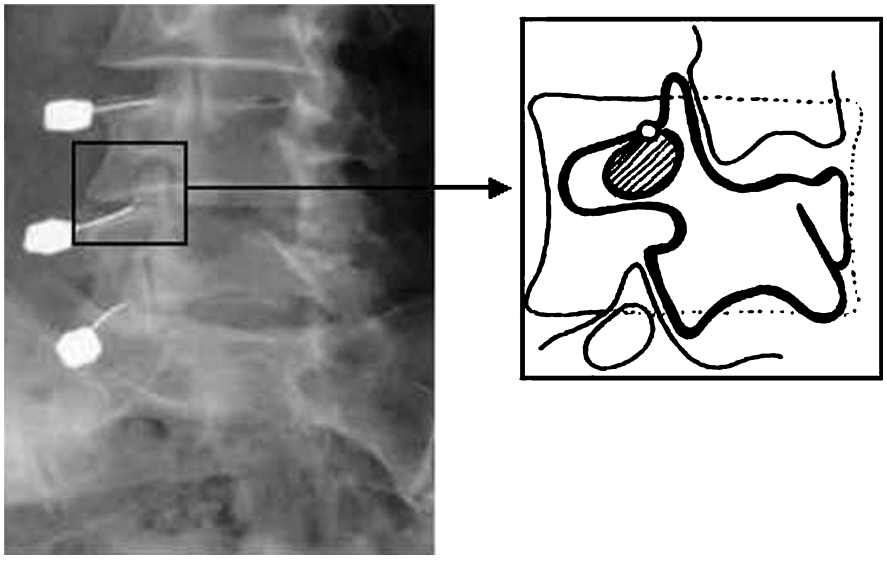

Fig. 1. Lumbar spine X-ray showing correct target for percutaneous radiofrequency block on the posterior primary rami. Radiofrequency needles are inserted at a point 5 cm lateral to the spinous process maintaining an angle of about 10–15 degrees between needles and horizontal plane and advanced to the point encountered at the superior articular process and transverse process (Burton's point)

an RF probe to interrupt the PPR of the segmental nerve in patients with facetal joint pain in the lumbar area [4]. As technology of electrode needles and imaging modalities are highly developed, the PRN technique is applied to structures as present in the anterior space of the vertebrae and intervertebral disc. This method has many advantages. Most important is a good circumscription of lesion with easy control of heat production. So there is no heat transmission other than in the target area. Another advantage of this technique includes precise selection of involved or targeted neural structures using the electric resistance of tissue, sensory and motor stimulation. This method seems to provide prolonged pain relief in patients who showed good response to previous PRN, then had symptoms recurred. In this case, good response, like that of previous PRN, will be anticipated. As newer, safer, and more convenient methods are being introduced, indications of RF technique will be widening.

In our study, there was no complication such as deafferentation pain after PRN. But 68 patients (29.8%) experienced temporary irritating feeling on the back after PRN for 2–7 days. So additional prescription of medication for this period may be needed and preoperative notice is appropriate.

We verified facetal originated pain using the presence of sign of ''4'', local paravertebral tenderness, and percussion tenderness. As cause of the difference in duration of pain relief between the two groups it was considered that chronic nonspecific low back pain was originated from multiple factors. When multiple causes induced patient's pain, besides facet joints, PRN had just temporary effects. With passing time, patient's pain would reappear or progress. But if the facet joints are the cause of chronic low back pain, long term pain relief will be achieved, as have shown our results. Hence PRN should be chosen depending on whether the cause of chronic back pain was originated from facet or not. The most important factor that decides on good therapeutic response and prognosis is proper patient selection.

When evaluating the therapeutic efficacy of PRN, immediate responders anticipate good results. However, some patients (48 patients, 21% of this study) showed therapeutic response 2–3 weeks later. Therefore it is desirable that clinical result should not be confirmed by immediate response only. Clinical result should be confirmed at minimum 4 weeks later.

Conclusion

PRN on PPR is a simple and safe procedure. This method seems to provide prolonged pain relief and functional recovery in appropriately selected patients with minimal side effects. So this method may be utilized as a valid treatment modality in many patients with facetal originated pain (facet syndrome). This therapy has many advantages, such as good effect, cost-effectiveness, safety, and repeatability. But as was shown in this study, long term pain relief cannot be anticipated in patients suffering from chronic low back pain with nonspecific cause. To achieve good long-term results, one should make an effort to properly select the patients with facet joints related low back pain and acquire knowledge about anatomy, RF treatment and experience.

References

1. Bogduk N (1983) The innervation of the lumbar spine. Spine 8: 286–293
2. Schwarzer AC, Aprill CN, Derby R, Fortin J, Kine G, Bogduk N (1994) The false-positive rate of uncontrolled diagnostic blocks of the lumbar zygapophysial joints. Pain 58: 195–200
3. Schwarzer AC, Wang SC, Bogduk N, McNaught PJ, Laurent R (1995) Prevalence and clinical features of lumbar zygapophysial joint pain: a study in an Australian population with chronic low back pain. Ann Rheum Dis 54: 100–106
4. Shealy CN (1975) Percutaneous radiofrequency denervation of spinal facets: treatment for chronic back pain and sciatica. J Neurosurg 43: 448–451

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Chronic deep brain stimulation of subthalamic and anterior thalamic nuclei for controlling refractory partial epilepsy

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Summary

Objectives. Experimental data and case reports of intractable epilepsy patients treated with deep brain stimulation (DBS) of the internal nuclei suggest a considerable anticonvulsant effect. We intended to describe the results of DBS on subthalamic nuclei and anterior thalamic nuclei (STN and ATN) from our patients and to evaluate the long-term efficiency and safety of DBS for controlling intractable epilepsy.

Methods. Six patients with refractory epilepsy and inadequate for surgery were implanted with DBS electrodes (3 in STN and 3 in ATN, respectively), switched on after a week of insertion followed by chronological observation. Seizure counts were monitored and compared with pre-implantation baseline.

Results. There was significant clinical improvement in respect of reduction of seizure frequency as well as the alleviation of ictal severity in almost patients. The mean reduction in seizure frequency was 62.3% (49.1% from STN vs. 75.4% from ATN). Except one patient (*patient 3*) with accidental infection on the right anterior chest, no complication or withdrawal of DBS was seen during our study.

Conclusion. DBS on STN and ATN demonstrated their clear efficiency and relative safety comparable or superior to previous studies during long term follow-up. Subsequent, well designed studies warrant the further increase of the knowledge about antiepileptic effect of DBS.

Keywords: Deep brain stimulation; subthalamic nucleus; anterior thalamic nucleus; refractory epilepsy.

Introduction

About thirty percent of the patients with epilepsy who are treated with antiepileptic drugs continue to have refractory seizures [16]. Respective surgery is considered as a therapeutic option if the seizures have a focal epileptogenic zone and presurgical evaluation clearly demonstrates that the area can be removed without causing neurological deficits. But, up to 40% of these cases are proven to be unsuitable for surgery because of the involvement of the eloquent areas or because of the bilateral or multifocal nature of the ictal onset [15]. Recently, a variety of brain structures that were thought to modulate cortical excitability have been stimulated for the purpose of improving seizure severity [3, 5, 6, 8, 11, 12, 17, 25–27]. Among them, the subthalamic nucleus (STN), which has a lot of accumulated human experience from Parkinson's disease (PD) for more than ten years and anterior thalamic nucleus (ATN) have been shown to be a safe and effective loci for controlling the intractable partial seizures from some patients [3, 5, 11, 12].

STN stimulation for epilepsy treatment has a basis from some experimental evidence of the subcortical network that influences cortical excitability – namely, nigral control of the epilepsy system (NCES) [9].

The role of ATN in the pathogenesis of seizure generalization is confirmed by the findings of increased metabolic activity in ATN during seizures and high frequency stimulation (HFS) of ATN and its afferent pathways can reduce seizures in the experimental animal studies [18–20].

Functional neuroimaging techniques have provided much information on the anatomic correlates of neurologic disorders [14], and there is growing evidence that different behavioral variables are represented differentially along distinct corticobasal ganglia circuits [1, 7]. We have previously shown that cerebral perfusion increase at the irritative zones of epilepsy patients is associated with favorable seizure reduction after HFS on STN in two cases of frontal lobe epilepsy (FLE) [24].

The aim of this study was to describe the results of chronic deep brain stimulation (DBS) on the deep nuclei (STN and ATN, respectively) from our patients and to evaluate the long-term efficiency and safety of DBS for controlling intractable epilepsy.

Patients and methods

Six patients with refractory epilepsy were implanted with DBS electrodes (three patients in the bilateral STN, the other 3 in bilateral ATN), switched on after a week of insertion and followed up for 2–30 months (mean 13.2 months). Two of STN DBS patients had a FLE (one with bilateral onset, the other with right sided onset). The other STN DBS patient had a temporal lobe epilepsy (TLE) of bilateral temporal onset. The surgical procedures and follow-up methods of STN DBS were described previously [24].

Two out of three patients with ATN DBS had non-lateralizing FLE. The last patient with ATN DBS was multifocal epilepsy from diffuse malformation of cortical development. We used Medtronic 3387 leads in ATN DBS and the target side was identified on each side by visual selection with reference to a standard stereotactic atlas under microelectrical recording of ATN and dorsomedial nucleus (DM) of thalamus. The EEG recording during the insertion of electrodes with or without external electrical stimulation (slow frequency; 5–10 Hz, intensity; 3–7 V, pulse width 90 μs) followed by connection of internal pulse generator (IPG) was performed as the method of STN DBS [24]. For chronic ATN HFS, we used a cycling stimulation on each side set to deliver 1 min on/5 min off, alternating left and right sides. Initially, monopolar current was provided with the pulse width of 90 μsec, and the frequency was set at 130 Hz. Stimulation parameter was adjusted for a satisfactory clinical response, determined individually for each patient.

Results

General results

After the chronic DBS, all of patients except one (patient 2) showed the >50% decrease in seizure frequency relative to the baseline value. Two patients with ANS DBS had seizure reduction >85%. Except one patient (patient 3), no major morbidity was developed during DBS period. Patient 3 had accidental, significant infection around the IPG insertion site and we stopped stimulation and removed the DBS device from him. No stimulation-induced side effects were observed. Families of three patients reported improvements in cognitive and behavioral status during daily living, and we previously reported the one example from patient 2 [24]. The overall results from our patient's seizure reduction ranged from 20 to 90.7%, with a mean of 62.3% (Table 1). In patient 3, the ratio was seizure frequency just before the removal of DBS devices compared with the baseline value.

Individual patients

Patient 1

A 23-year-old woman with global cognitive dysfunction was selected for STN DBS. Regardless of the previous respective surgery on the right frontal cortex with anterior callosotomy after a series of invasive study four years before, the refractory seizures were still continued. She displayed frequent bilateral asymmetric tonic seizures (left > right) with rare drop attacks, and mean seizure frequency was 15/month. Interictal EEG showed bilaterally independent and bilaterally synchronous generalized spike-and-wave discharges; maximal over the frontal regions with slight right side dominance and the ictal onset EEG showed generalized electrodecremental response followed by irregular spike-and-wave with briefly right hemispheric dominance, progressing to obscuration by movement artifacts. Her antiepileptic drugs (AED) were valproate, carbamazepine, topiramate and oxcarbazepine. Continuous monopolar STN stimulation started electrode at bilateral 3−, with the amplitude of 2.0 V and pulse width 60 μsec. The parameter of stimulation was changed according to the seizure frequency and intensity (1− to 3−, 2 to 3.2 V, 60 to 120 μsec), but no significant differences were seen with any of the parameter changes. At the moment of postoperative 30 month, the seizure had decreased to 56% of her baseline value and valproate and oxcarbazepine was successfully discontinued as well.

Patient 2

A 22-year-old male patient was admitted for DBS of the STN. Previously, he had undergone right cortical

Table 1. *Results of DBS of STN and ATN for Epilepsy in CMCK*

Patient	Localization of seizure onset	Site of insertion	Age (yr)	F/U (M)	Baseline seizure number/M	Seizure reduction
1	bilateral frontal, poorly localized	STN	23	30	15	56%
2	right frontal, diffuse	STN	22	18	75	20%
3	bilateral independent temporal	STN	14	loss d/t infection	42	71.4% (postop. 1 M)
4	bilateral anterior frontal	ATN	28	10	15	85.7%
5	bilateral frontal, poorly localized	ATN	23	6	15	90.6%
6	multifocal, poorly localized	ATN	14	2	450	50%
	average		20.7	11.2	102	62.3%

CMCK Catholic medical center of Korea, *STN* subthalamic nucleus, *ATN* anterior thalamic nucleus, *d/t* due to, *postop.* postoperative.

resection to relieve the frequent, brief hypermotor seizures with fencing posture that was suspected to originate from the right supplementary motor area (SMA). Interictal spikes were found in the right hemisphere with a right frontal dominance and during ictal onset period, the brief polyspikes or fast activity on both fronto-central areas (R > L, FC2 max) were followed by severe movement artifacts. However, he showed little clinical improvement after incomplete resection of the extensive epileptogenic zone. The seizure frequency was 2.5/day on the average despite of six AED medications. Bilateral continuous STN stimulation with the parameter (both 1−, 0.8 V, 130 Hz, 60 μsec) was started. Regardless of the various stimulation parameter (monopolar to bipolar, 0.8 V to 3 V, 60 μsec to 90 μsec), his seizure frequency and intensity was not reduced significantly. The reduction rate of seizure frequency at the last visit was about 20% comparing to frequency at the pre-stimulation period.

Patient 3

A 14-year-old boy with global cognitive delay and frequent automotor and hypermotor seizures with secondary generalization from bilateral independent foci of temporal lobe was selected for STN DBS. His seizure frequency was 1–2 per day and not controlled with topiramate, lamotrigine, valproate and vigabatrine. After insertion of electrode, marked reduction of seizure frequency and intensity was found. The ratio of 71.4% seizure reduction was seen after 3 weeks switched on. But, at 5 weeks after insertion, unexpected inflammation and discharges around the wound site of IPG on the R anterior chest was detected. Immediate and massive antibiotic therapy for 2 weeks was in vain and removal of IPG and all the other hardware after 50 days from electrodes insertion. The causative organism was *Staphylococcus aureus* detected from his wound infection site of the right anterior chest.

Patient 4

A 28-year-old woman with frequent dialeptic seizure and intermittent automotor seizure was admitted for ATN DBS. Her interictal spikes were seen in both the anterior frontal and L fronto-temporal areas. Ictal onset was fast rhythm poorly lateralized and appearing maximal in both frontal areas, that ultimately builds up in L hemisphere with fronto-temporal maximum. She refused invasive surgery and subsequent resective surgery for fear of the possible neurological sequelae. Mean seizure frequency of pre-insertional state was once per two days, but after insertion of ATN electrodes, marked reductions of seizure frequency were found. Monopolar, bilateral stimulation on lead 2− was continued with intensity of initial 1.5 V to the last 2.4 V, and the other parameter was described above. Ten months after initiation of ATN DBS, her seizure frequency was still continued once per 2 weeks (85.7% reduction).

Patient 5

A 23-year-old man with previous craniectomy for the resection of medulloblastoma in the cerebellum was admitted for the control of his frequent intractable secondarily generalized seizures. The seizure frequency was 0.5/day and the interictal EEG showed bilateral, multiregional independent spikes or diffuse spike-and-waves maximal over frontal areas. Ictal onset was not lateralized but dominant at the frontal areas and progressed to rapid generalization. Monopolar bilateral stimulation over ATN was started on both the 1− leads with 1.5 V intensity. Six months after the stimulation, the seizure frequency was definitely reduced to 9.4% of baseline ratio (90.6% reduction).

Patient 6

A 14-year-old female patient with brief, frequent tonic seizures over the trunk and R arm was admitted. Brain MRI showed wide-spread band heterotopia around the lateral ventricles, and interictal and ictal EEG revealed multiregional irritative zones as well as diffuse ictal onset zone. Her seizure frequency was 10–30 per day with predilection of occurrence during morning period. During the seizure, she had usually experienced loss of consciousness for a few to ten seconds, but no secondarily generalized convulsion was found. After ATN electrodes insertion and switch on, she has experienced markedly shortened seizure duration (about 1–2 seconds) and about 50% reduction of seizure frequency for the subsequent 2 months. The long term follow-up should be warranted.

Discussion

Recently, several methods of DBS in refractory epilepsy have been tried and followed in some specialized epilepsy centers. First, the earliest trials were to target crucial structures that are considered as a ‘‘pacemaker’’ or to have an essential role in epileptogenic networks, such as the thalamus or the subthalamic nucleus (‘indirect’ method). Second approach was to interfere with the area

of ictal onset itself (ex. Hippocampus) and prevent the propagation of the seizure ('direct' method). The other method is to deliver the therapeutic electrical stimulation in response to a cue of ictal onset with the use of seizure-detecting or predicting algorithms (Closed-loop systems) [22, 23].

The mechanism of therapeutic action of DBS in reducing seizures remains unclear. But, some different explanations have been proposed. First, DBS may act by blocking local neuronal activity because DBS produces clinical effect similar to that from lesion provoked by the insertion of the electrode itself (microthalamotomy) [11]. A second theory holds that DBS acts through local inhibition induced by current applied to a specific CNS structure. This is the hypothesis of the so-called reversible functional lesion, where in the case of targeting crucial structures in a network, nuclei that are involved in propagating, sustaining, or triggering epileptic activity are inhibited [28]. Our previous paper demonstrated that increased cerebral perfusion areas after STN DBS corresponding to the patient's irritative zones provided a clue to understand the mechanism of DBS in epilepsy [24]. But, in the cases of ATN DBS, similar findings were not shown (not described in this paper). But, the additive results from ongoing functional imaging studies of our patients would provide more convincing answers to solve the problem.

Our patients showed a mean reduction in seizure frequency of 62.3% (49.1% from STN vs. 75.4% from ATN), which are comparable or superior (especially, the results from ATN DBS) to the previous human studies [2, 3, 11, 12]. And it may be oversimplified that the ATN DBS is more suitable than the STN DBS for controlling seizures from partial intractable epilepsy. However, the number of patients treated so far is too small to allow any conclusions.

We had a regretful experience of removal of DBS devices from the accidental wound infection with patient 3, who had shown great improvement of cognitive status and activities of daily living as well as a prominent reduction of seizure frequency. Deep-brain implantation usually is associated with a low incidence of infection ranged from 0 to 10.6% per electrode [4, 10, 13, 21]. The causative organisms most often implicated in DBS hardware infections are staphylococcus, enterobacter, streptococcus, pseudomonas and rarely mycobacterium or candida [21]. Causative bacteria are usually from the patient's skin flora. The other five of our patients have not shown any complications related to hardware or during the DBS parameter change.

Conclusion

In our uncontrolled study of DBS on structures indirectly connected to epileptogenic areas (STN and ATN), we could identify their efficiency and relative safety comparable or superior to previous studies during long-term follow up. Future controlled studies in larger patient series are warranted to increase the knowledge about antiepileptic effects of DBS.

References

1. Alexander GE, Crutcher MD, De Long MR (1990) Basal ganglia-thalamocortical circuits: parallel substrates for motor, oculomotor, prefrontal and limbic functions. Prog Brain Res 85: 119–146
2. Benabid AL, Koudsie A, Chabrdes S (2004) Subthalamic nucleus and substantia nigra pars reticulate stimulation: the Grenoble experience. In: Luders HO (ed) Deep brain stimulation and epilepsy. Martin Dunitz, London
3. Benabid AL, Minotti L, Koudsie A, de Saint Martin A, Hirsch E (2002) Antiepileptic effect of high-frequency stimulation of the subthalamic nucleus (corpus Luysi) in a case of medically intractable epilepsy caused by focal dysplasia: a 30-month follow-up: technical case report. Neurosurgery 50: 1385–1392
4. Beric A, Kelly PJ, Rezai A, Sterio D, Mogilner A, Zonenshayn M, Kopell B (2001) Complications of deep brain stimulation surgery. Stereotact Funct Neurosurg 77: 73–78
5. Chabardes S, Kahane P, Minotti L, Koudsie A, Hirsch E, Benabid AL (2002) Deep brain stimulation in epilepsy with particular reference to the subthalamic nucleus. Epileptic Disord 4: 83–93
6. Chkhenkeli SA, Chkhenkeli IS (1997) Effects of therapeutic stimulation of nucleus caudatus on epileptic electrical activity of brain patients with intractable epilepsy. Stereotact Funct Neurosurg 69: 221–224
7. Devous MD (1995) SPECT functional brain imaging. Technical considerations. J Neuroimaging 1S: 2–13
8. Fisher RS, Uematsu S, Krauss GL, Cysyk BJ, McPherson R, Lesser RP, Gordon B, Schwerdt P, Rise M (1992) Placebo-controlled pilot study of centromedian thalamic stimulation in treatment of intractable seizures. Epilepsia 33: 841–851
9. Gale K, Iadarola MJ (1980) Seizure protection and increased nerve-terminal GABA: delayed effects of GABA transaminase inhibition. Science 208: 288–291
10. Hariz MI (2002) Complications of deep brain stimulation surgery. Mov Disord 17 [Suppl] 3: 162–166
11. Hodaie M, Wennberg RA, Dostrovsky JO, Lozano AM (2002) Chronic anterior thalamus stimulation for intractable epilepsy. Epilepsia 43: 603–608
12. Kerrigan JF, Litt B, Fisher RS, Cranstoun S, French JA, Blum DE, Dichter M, Shetter A, Baltuch G, Jaggi J, Krone S, Brodie M, Rise M, Graves N (2004) Electrical stimulation of the anterior nucleus of the thalamus for the treatment of intractable epilepsy. Epilepsia 45: 346–354
13. Kondziolka D, Whiting D, Germanwala A, Oh M (2002) Hardware-related complications after placement of thalamic deep brain stimulator systems. Stereotact Funct Neurosurg 79: 228–233
14. Krause M, Fogel W, Heck A, Hacke W, Bonsanto M, Trenkwalder C, Tronnier V (2001) Deep brain stimulation for the treatment of Parkinson's disease: subthalamic nucleus versus globus pallidus internus. J Neurol Neurosurg Psychiatry 70: 464–470
15. Kwan P, Brodie M (2000) Early identification of refractory epilepsy. N Engl J Med 342: 314–319

16. Lesser RP (1999) Unexpected places: how did vagus nerve stimulation become a treatment for epilepsy? Neurology 52: 1117–1118
17. Loddenkemper T, Pan A, Neme S, Baker KB, Rezai AR, Dinner DS, Montgomery EB Jr, Luders HO (2001) Deep brain stimulation in epilepsy. J Clin Neurophysiol 18: 514–532
18. Mirski MA, Ferrendelli JA (1986) Anterior thalamic mediation of generalized pentylenetetrazol seizures. Brain Res 399: 212–223
19. Mirski MA, Ferrendelli JA (1994) Electrical stimulation of the mammillary nuclei increases seizure threshold to pentylenetetrazol in rats. Epilepsia 35: 1309–1316
20. Mirski MA, Rossell LA, Terry JB, Fisher RS (1997) Anticonvulsant effects of anterior thalamic high frequency electrical stimulation in the rat. Epilepsy Res 28: 89–100
21. Oh MY, Abosch A, Kim SH, Lang AE, Lozano AM (2002) Long term hardware-related complications of deep brain stimulation. Neurosurgery 50: 1268–1276
22. Osorio I, Frei MG, Giftakis J, Peters T, Ingram J, Turnbull M, Herzog M, Rise MT, Schaffner S, Wennberg RA, Walczak TS, Risinger MW, Ajmone-Marsan C (2002) Performance reassessment of real-time seizure-detection algorithm on long ECoG series. Epilepsia 43: 1522–1535
23. Osorio I, Frei MG, Sunderam S, Giftakis J, Bhavaraju NC, Schaffner SF, Wilkinson SB (2005) Automated seizure abatement in humans using electrical stimulation. Ann Neurol 57: 258–268
24. Shon YM, Lee KJ, Kim HJ, Chung YA, Ahn KJ, Kim YI, Yang DW, Kim BS (2005) Effect of chronic deep brain stimulation of the subthalamic nucleus for frontal lobe epilepsy: subtraction SPECT analysis. Stereotact Funct Neurosurg 83: 84–90
25. Velasco F, Velasco M, Ogarrio C, Fanghanel G (1987) Electrical stimulation of the centromedian thalamic nucleus in the treatment of convulsive seizures: a preliminary report. Epilepsia 28: 421–430
26. Velasco M, Velasco F, Velasco AL, Menes D, Gordon F, Rocha L, Briones M, Marquez I (2000) Subacute electrical stimulation of the hippocampus blocks intractable temporal lobe seizures and paroxysmal EEG activities. Epilepsia 41: 158–169
27. Vonck K, Boon P, Achten E, De Reuck J, Caemaert J (2002) Long-term amygdalohippocampal stimulation for refractory temporal lobe epilepsy. Ann Neurol 52: 556–565
28. Vonck K, Boon P, Claeys P, Dedeurwaerdere S, Achten R, Van Roost D (2005) Long-term deep brain stimulation for refractory temporal lobe epilepsy. Epilepsia 46 [Suppl] 5: 98–99

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Vagus nerve stimulation in pediatric intractable epilepsy: a Korean bicentric study

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Summary

Objective. To present our experience with vagus nerve stimulation (VNS) and to evaluate the long-term efficacy and safety of the procedure in pediatric intractable epilepsy.

Methods. This study included sixteen patients, who were implanted with a vagus nerve stimulator and could be followed up for at least more than 12 months in two epilepsy centers. Data including seizure frequency, EEG, quality of life measures and adverse events were prospectively filed over a 5-year period.

Results. VNS resulted in a >50% reduction in seizure frequency in 50.0% (8/16) of children with 31.3% (5/16) of patients achieving a >90% reduction. Additionally, enhancements in quality of life were as follows: memory in 50.0% (8/16), mood in 62.5% (10/16), behavior in 68.8% (11/16), alertness in 68.8% (11/16), achievement in 37.5% (6/16), and verbal skills in 43.8% (7/16) of the patients. Adverse events included hoarseness in two patients, dyspnea during sleep in two patients, and sialorrhea in one patient. However, these events were tolerable or could be controlled by the adjustment of output currents. In one patient, wound revision was required.

Conclusion. Our data supports the role of VNS as an alternative therapy for pediatric intractable epilepsy.

Keywords: Vagus nerve stimulation; pediatric intractable epilepsy.

Introduction

In 1938, Bailey and Bremer discovered that vagus nerve stimulation (VNS) in cats induced changes in electroencephalograms (EEGs), and the first human stimulator was introduced in 1988 [1]. Currently, VNS is accepted as one of the therapeutic modalities applicable to patients who prove refractory to standard medical treatment. Moreover, due to the possible effects of drug therapies on development in children and adolescents, more than a quarter of the approximately 30,000 patients with implanted vagus nerve stimulators have been younger than 18 years [10]. In Korea, the first implantation was performed in 1999 after Korean FDA approval but it has only been recently that medical insurance has covered VNS therapy.

We report on our experience of this relatively new technique and its long-term efficacy and safety in pediatric intractable epilepsy.

Patients and methods

The subjects of this study included 16 pediatric patients who had a vagus nerve stimulator implanted for intractable epilepsy at the Epilepsy Centers in Sang-gye Paik Hospital and Severance Hospital in Korea. Patients varied in seizure etiology, seizure type and epilepsy syndrome. These patients had been experiencing more than four seizures per month and the seizures were not controlled by the initial combination of two or more anti-epileptic drugs (mean $\pm$ SD, 3.6 ± 1.1). These patients were also ineligible for epileptic surgery due to multifocal or generalized epileptic foci. All subjects began VNS therapy in July 1999 and ended therapy in July 2004. The patients could be followed up for at least more than 12 months. Since the first implantation, data including seizure frequency, EEG, quality of life measures, and adverse events were prospectively collected and filed for 5 years.

Initial device parameters included: 0.25 mA output current, 30 Hz frequency, 500 μs pulse width, on 30 seconds/off 5 minutes, and were set and adjusted in accordance with the guidelines suggested by Cyberonics, Inc. (Houston, TX). The parameters were also tailored to each patient's individual requirements (Fig. 1).

The MedCalc program was used for statistical analysis. We used the Student's *t*-test to evaluate the significant differences between dependent and continuous variables. A p value <0.05 was regarded as statistically significant.

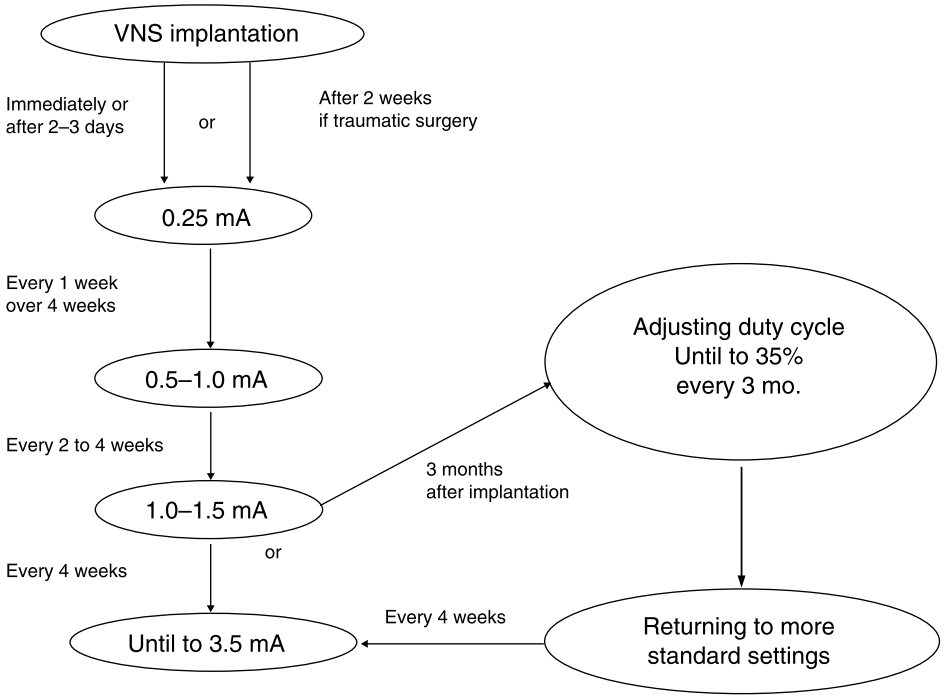

Fig. 1. Recommended protocol of VNS parameter settings by Cyberonics, Inc. (Houston, TX)

Results (Table 1)

The mean age (±SD) of the 16 patients (8 male and 8 female) at the initiation of VNS was 9 years 3 months (±54.1 months) (age range, 2 years 5 months–17 years 11 months). The mean duration of a seizure (±SD) before implantation was 6 years 10 months (±58.8 months) (range, 1 year 5 months–17 years 10 months). Mean follow-up duration after implantation was 31 months (±21.2 months) (range, 12 months–6 years 7 months). Seizure type and epilepsy syndrome included: 11 patients with Lennox-Gastaut syndrome (LGS), three patients with complex partial seizure, one patient with severe myoclonic epilepsy in infancy and one patient with gelastic seizure originating from hypothalamic hamartoma. The other detailed demographics and clinical characteristics are presented in Table 1.

The VNS resulted in a >50% reduction in seizure frequency in 50.0% (8/16) of children with 31.3% (5/16) patients achieving a >90% reduction at the last follow-up after implantation. There were no significant differences according to etiology. However, two patients (Patients 1 and 5) with complex partial seizure and LGS from tuberous sclerosis complex, respectively, showed a seizure reduction of >90%. One patient (Patient 15) with gelastic seizure from hypothalamic hamartoma failed to respond to VNS during 44 months of treatment. Of the eight patients who achieved favorable seizure outcomes with a seizure reduction of >50%, two patients (Patients 9 and 16) showed a gradual seizure reduction during the initial 12 months after stimulation. However, the other six patients maintained the initial efficacy for three months and did not show improved seizure outcomes after that time. A brief reduction in seizure severity by magnetic stimulation of the device was observed in only two patients, one patient (Patient 9) with LGS from pachygyria and one patient (Patient 16) with complex partial seizure from hypoxic ischemic encephalopathy. In three patients, output current was increased up to 3.25 mA, but high output current failed to obtain further reduction of seizure frequency. Duty cycle was also adjusted from 10 to 35% in six patients but did not induce the anticipated seizure outcomes, necessitating a change back to previous duty cycle. Antiepileptic medication could be reduced by one or two drugs in four patients who showed a seizure reduction of >90%. However, even these patients should maintain single or double antiepileptic drug therapy.

After VNS therapy, the patients' EEGs showed no interval changes in most cases. However, in two patients, the stimulator induced favorable EEG changes. In one patient (Patient 7) with LGS obtained complete seizure ablation, and the EEG showed improvement of background rhythms with much less frequent generalized epileptiform discharges compared with previous tracing.

Table 1. *Demographics and clinical characteristics of the study group*

No. of pt/sex	Age at start of VNS (mo.)	Duration of VNS (mo.)	Epilepsy syndrome	Seizure types	Aetiology	Last seizure outcomes* (%)	EEG changes	Adverse events
Pt 1/M	71	12	CPS	Dileptic seizure	TS	90		
Pt 2/M	165	12	SMEI	GTC	cryptogenic	25		hoarseness
Pt 3/F	64	12	LGS	Atonic seizure	cryptogenic	25		
Pt 4/F	104	12	CPS	Focal TC	cryptogenic	75		
Pt 5/F	33	15	LGS	GT	TS	90	normalized	
Pt 6/M	65	18	LGS	GT	Mitochondrial cytopathy	0		
Pt 7/M	29	21	LGS	MC	Cryptogenic	100	rare GED	
Pt 8/F	139	21	LGS	Atonic seizure	Band heterotopia	25		
Pt 9/M	139	25	LGS	GTC, GT, atypical ABS	Pachygyria	100†		
Pt 10/M	40	26	LGS	Atonic, atypical ABS, Focal clonic	Cryptogenic	25		
Pt 11/F	85	31	LGS	Atonic	Cryptogenic	50		
Pt 12/F	76	49	LGS	atypical ABS, GT	Cryptogenic	25		dyspnea
Pt 13/M	92	61	LGS	MC, atypical ABS	Encephalitis	50		
Pt 14/F	215	79	LGS	MC, atypical ABS	Cryptogenic	25		sialorrhea
Pt 15/F	177	44	CPS	gelastic seizure	hypothalamic hamartoma	0		generator malfunction
Pt 16/M	87	61	CPS	focal TC	HIE	90†		hoarseness, dyspnea, wound infection

Pt Patient; *VNS* vagus nerve stimulation; *CPS* complex partial seizure; *SMEI* severe myoclonic epilepsy in infancy; *LGS* Lennox-Gastaut syndrome; *GTC* generalized tonic clonic; *TC* tonic clonic; *GT* generalized tonic; *MC* myoclonic; *ABS* absence; *TS* tuberous sclerosis; *HIE* hypoxic ischemic encephalopathy; *GED* generalized epileptiform discharges.

* A reduction of seizure frequencies patient who had effect of magnetic stimulation, † patient who had effect of magnetic stimulation.

In addition, one patient (Patient 5) with LGS from tuberous sclerosis complex showed complete cessation of epileptic discharges with a seizure free state.

We compared the five quality of life variables between baseline and follow-up at an interval of 12 months until the follow-up endpoint. Quality of life measures improved as follows: memory in 50.0% (8/16), mood in 62.5% (10/16), behavior in 68.8% (11/16), alertness in 68.8% (11/16), achievement in 37.5% (6/16), and verbal skills in 43.8% (7/16) of the patients.

One or more complications were observed in four patients. One patient (Patient 16) developed hoarseness after 12 months at an output current of 2.25 mA, and again after 21 months at output current of 2.0 mA. In each episode, symptoms were controlled after the reduction of the output current by 0.25 mA. This particular patient also developed wound infection at the operation site and the infection healed after revision of the wound site. Another patient (Patient 14) reported excessive salivation at 3 months, but this symptom subsided after clinical observation. One patient (Patient 12) complained of a sense of mild dyspnea during sleep, but this improved after follow-up without any changes in the device settings. Only one patient (Patient 15) showed generator malfunction after 44 months, and device removal was necessary in this case. No adverse side effects such as bradycardia or arrhythmia were observed during implantation or the test run of the device in the operating room.

Discussion

The non-pharmacologic aspects of VNS therapy make it particularly attractive for use due to the side effects and cognitive impairments associated with anticonvulsants; and in pediatric patients side effects can include mental retardation and delayed development [10]. Further studies are needed to support the earlier use of VNS therapy in the treatment course of children with intractable seizures.

Several recent studies have examined the efficacy of VNS therapy in children. Helmers *et al.* [3] reported that 30% of patients had more than a 75% decrease in seizure frequency at 6 months after VNS implantation and Murphy *et al.* [5] reported that 45% of patients achieved greater than a 50% reduction. Although the number of samples is too small to draw any statistical conclusions, our results agree with previous reports studying other VNS patient groups. It has been known that patient improvement does not appear to be dependent on seizure

type or cause [3]. Parain *et al.* [7], however, reported that half (5/10) of the patients with tuberous sclerosis complex showed a seizure reduction of >90%, and we found similar results in both patients with tuberous sclerosis complex in our study. Contrary to a previous report [6], the patient with gelastic seizure from hypothalamic hamartoma did not show favorable results after VNS therapy in our study. Similar to previous long-term results in an adult population [2], two patients in our study showed improvements in seizure frequency that increased with time. However, in the other patients, the initial efficacy during the first 3 months of VNS therapy was the most important predictive factor for the long-term efficacy of VNS therapy.

Although EEG changes resulting from VNS therapy have been controversial, Koo [4] reported the occurrence of EEG changes by a mechanism of the alternating synchronization and desynchronization. In this study, we observed significant improvements in the background and reduction of generalized epileptiform discharges after long-term treatment with vagus stimulation in two patients with LGS.

In addition to seizure reductions, our patients also show improvements in quality of life measures, including mood, alertness, verbal skills, memory, and school/professional achievements. Recent studies evaluating VNS therapy in children and adolescents showed similar results of improved quality of life and suggested that such improvements in quality of life are not solely due to improved seizure control [6, 8, 9].

Common adverse events reported by VNS therapy patients, including voice alterations, coughing during stimulation, and drooling have also occurred in the pediatric population [3]. A few patients have reported an increase in hyperactivity, which is a side effect unique to this age group [10]. In our patients, previously reported common complications such as hoarseness, dyspnea at sleep, sialorrhea were noted. Most of these side effects were transient or could be controlled by the adjustment of current output.

In conclusion, VNS is a safe and effective procedure. The most significant advantage of VNS is the absence of adverse effects on cognitive functions, which are the major drawbacks to the use of antiepileptic drugs, particularly in pediatric patients who are undergoing critical stages of neural development.

References

1. Bailey P, Bremer F (1938) A sensory cortical representation of the vagal nerve. J Neurophysiol 1: 4405–4412
2. DeGiorgio CM, Schachter SC, Handforth A, Salinsky M, Thompson J, Uthman B *et al* (2000) Prospective long-term study of vagus nerve stimulation for the treatment of refractory seizures. Epilepsia 41: 1195–1200
3. Helmers SL, Wheless JW, Frost M, Gates J, Levisohn P, Tardo C *et al* (2001) Vagus nerve stimulation therapy in pediatric patients with refractory epilepsy: retrospective study. J Child Neurol 16: 843–848
4. Koo B (2001) EEG changes with vagus nerve stimulation. J Clin Neurophysiol 18(5): 434–441
5. Murphy JV, Torkelson R, Dowler I, Simon S, Hudson S (2003) Vagal nerve stimulation in refractory epilepsy: the first 100 patients receiving vagal nerve stimulation at a pediatric epilepsy center. Arch Pediatr Adolesc Med 157: 560–564
6. Murphy JV, Wheless JW, Schmoll CM (2000) Left vagal nerve stimulation in six patients with hypothalamic hamartomas. Pediatr Neurol 23: 167–168
7. Parain D, Penniello MJ, Berquent P, Delangre T, Billard C, Murphy JV (2001) Pediatr Neurol 25: 213–216
8. Patwardhan RV, Stong B, Bebin EM, Mathisen J, Grabb PA (2000) Efficacy of vagal nerve stimulation in children with medically refractory epilepsy. Neurosurgery 47: 1353–1357
9. Valencia I, Holder DL, Helmers SL, Madsen JR, Riviello JJ Jr (2001) Pediatr Neurol 25: 368–376
10. Wheless JW, Maggio V (2002) Vagus nerve stimulation therapy in patients younger than 18 years. Neurology 59[Suppl] 4: S21–S25

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Seizure control of Gamma Knife radiosurgery for non-hemorrhagic arteriovenous malformations

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Summary

Objectives. Although radiosurgery has been found to be a safe and effective alternative treatment, seizure outcome of arteriovenous malformation (AVM) radiosurgery has not been documented in detail. We report the effect of Gamma Knife radiosurgery (GKRS) on seizures associated with AVMs and discuss the various factors that influence the prognosis.

Material and methods. Between 1992 and 2004, 246 patients were treated with GKRS for AVMs at Kyung-Hee medical center. Forty five (17.0%) patients have non-hemorrhagic AVMs and presenting symptom was seizure. Two patients of all were excluded from this study due to loss of follow-up after radiosurgery. In this study, retrospective analysis of clinical characteristics, radiologic findings, radiosurgical seizure outcome were performed.

Results. There were 32 male and 11 female with age ranging from 10 to 74 years (mean 35 years). Type of seizure included: general tonic clonic ($n = 28$); focal motor or sensory ($n = 7$); partial complex ($n = 8$). The location of AVM was temporal ($n = 18$); frontal ($n = 9$); deep seated ($n = 7$); parietal ($n = 5$); occipital ($n = 4$). Follow-up period was from 8 months to 12 years (mean 46 months). Mean volume was 6.2 cc (2.7–20), mean marginal and maximal dosage was 19.5 (17–26) and 36.6 Gy (13–50). During follow-up after radiosurgical treatment, 23 (53.5%) of 43 patients were seizure-free, 10 (23.3%) had significant improvement, were unchanged in 8 (18.6%) and aggravated in 2 (4.6%) patients. In 33 patients, follow-up angiography or MRI was performed. Complete obliteration was achieved in 16 (49.0%) patients, partial obliteration in 13 (39.0%). Four were unchanged (12.0%). Of 33 patients with follow-up performed, 26 were followed for over 2 years. Eleven (84.6%) of 13 patients with complete obliteration were seizure-free ($p < 0.005$). Four (36.3%) of 13 with partial obliteration and unchanged remained seizure-free. Fifteen patients had experienced intractable seizure before radiosurgery. After radiosurgery, seizures disappeared in 8 (53%) patients. Seizure frequently decreased in 5 (33%) and 2 patients (14%) were unchanged but none was aggravated. Five (71%) of 7 patients with complete obliteration were seizure-free and 2 (40%) of 5 patients with partial obliteration were seizure-free.

Conclusion. Up to now, controversy about resective surgery or radiosurgery as treatment of seizure related to AVMs still remains. In this study, we experienced that Gamma Knife radiosurgery is commonly performed to treat AVMs and can improve symptomatic seizure associated with AVMs. To clarify the mechanism of seizure control in AVMs radiosurgery is difficult, but it seems to be closely related to hemodynamic effects after radiosurgery.

Keywords: Arteriovenous malformation; radiosurgery; seizure.

Introduction

Intracranial arteriovenous malformations (AVMs) are congenital vascular anomalies that typically present with hemorrhage, headache, or seizure [1, 24]. Intracranial hemorrhage causes morbidity and mortality in patients with AVM [1]. Various therapeutic alternatives are currently available for reducing the risk of bleeding from AVMs, and reported treatment results have been favourable in terms of overall morbidity and mortality.

Seizure is the second most common mode of presentation of cerebral AVMs; it occurs in approximately one-third of patients with AVMs [18], and response to an anticonvulsant drug is variable [22]. The reported incidence varies from 18 to 60% [2, 7, 13, 14, 17, 20, 21, 23, 25, 29]. However, compared with numerous reports concerning the risk of bleeding [7, 11, 19, 21, 30], the natural history of AVM in relation to the risk of seizure and factors influencing the seizure development remain less clear, and prognosis of seizure with AVMs has received little attention.

Approximately 50–80% of patients with seizure who underwent resection of the AVM had a significant reduction in seizure tendency after resective surgery [23]. Less than 10% of patients without a prior history of seizure activity will develop seizures postoperatively. But controversy exists over the surgical treatment of AVMs associated with seizure [23, 31, 32].

Currently, stereotactic radiosurgery is commonly performed as an alternative treatment for patients with high-risk AVMs. Stereotactic radiosurgery has been shown

to reduce seizure activity in selected patients with AVMs [18].

However, the outcome of AVM radiosurgery has not been documented in detail. In this study, we analyzed the characteristics and frequency of seizure in 43 patients with unruptured AVMs after radiosurgery. The effects of focused irradiation and hemodynamic change on seizures associated with AVMs are reported and the various factors that influence the prognosis are discuss.

Clinical material and methods

A total of 246 patients with an angiographically identified intracerebral AVM underwent stereotactic radiosurgery at our Gamma Knife center between March 1992 and March 2004. Sixty patients (24%) had experienced seizure before treatment. Forty-five of these sixty patients (75%) presented seizure as the initial symptom without hemorrhage or other clinical symptoms.

Two patients were excluded from this study due loss of follow-up after radiosurgery. A total of 43 patients were included in the present series. Patients' clinical information was obtained from their medical records (including hospital charts, physician notes, and correspondence) and direct patient contact. The diagnosis of seizure was established historically through patient interview, witness description if available, and electroencephalogram.

There were 32 male and 11 female patients with ages ranging from 10 to 74 years (median 35 years). Type of seizure were classified as: general tonic clonic ($n = 28$); focal motor or sensory ($n = 7$); or partial complex ($n = 8$). The AVM was located in temporal ($n = 18$); frontal ($n = 9$); deep seated ($n = 6$); parietal ($n = 5$); or occipital ($n = 4$). In addition, they were also analyzed according to seizure duration, nidus volume and seizure frequency (Table 1). The follow up period was from 8 months to 12 years (median 46 months). Clinical examination and radiologic findings (MRI or cerebral angiography) were performed at 6 months after radiosurgery. Ten patients had clinical and MRI follow-up but did not have follow-up angiography. All patients continued to take an anticonvulsant drug at radiosurgery. To investigate the development of new seizures after radiosurgery, we also undertook a retrospective survey of patients with no history of seizure, hemorrhage, neurologic deficit, or surgical resection treated in the same period (non-epileptogenic AVMs). There were no significant differences in the demographic characteristics of the patients between the epileptogenic and non-epileptogenic AVM groups.

Table 1. *Clinical characteristics of 43 patients*

Characteristics	Number of patients
Sex	
– Male	32
– Female	11
Location of AVM	
– Temporal	18
– Frontal	9
– Deep seated	7
– Parietal	5
– Occipital	4
Type of seizure	
– General tonic clonic	28
– Focal motor sensory	7
– Partial complex	8
Seizure frequency of pre-GKRS	
– 0–4	19
– >4	24
Duration of seizure history (yrs)	
– <1	19
– 1–5	11
– >5	13
Volume of AVM	
– <4 cc	21
– 4–10 cc	15
– >10 cc	7

Radiosurgical technique

Radiosurgery was performed using the Leksell Gamma Knife (Elekta instrument AB, Stockholm, Sweden). The definition of the nidus and localization of irradiation target dose were based on biplane stereotactic cerebral angiography and MRI. The radiation dose delivered to the margine of the nidus, and the number and configuration of the irradiation isocenters were determined jointly by neurosurgeons and radiation physicians. The volume averaged 6.2 cc (2.7–20). The mean isocenter and isoprofile was 2.8 (1–8) and 60.4% (40–80). The mean maximal and marginal dosage was 36.5 Gy (13–50) and 19.5 Gy (17–26).

Results

In 33 of 43 patients, follow up angiography was performed. Sixteen (49%) patients had complete obliteration, partial obliteration was found in 13 (39%) patients and 4 (12%) patients were unchanged.

Of the 43 patients with a seizure history before radiosurgery, 23 (53.5%) patients were classed as "seizure-free" at the last follow up examination. They were determined seizure-free if they had not experienced a seizure for at least 1 year at the final follow up examination, with or

Table 2. *Control rate of the seizure after Gamma Knife radiosurgery*

Seizure free		23 (53.5%)
– Without medication	3	
– With medication	20	
Seizure improved		10 (23.3%)
– Without medication	1	
– With medication	9	
Seizure unchanged		8 (18.6%)
Seizure aggravation		2 (4.6%)

Table 3. *Seizure outcome vs. 2 years angiographic obliteration*

	Complete obliteration	Partial obliteration	Unchanged
Seizure free	11 (84.6%)	4 (36.3%)	0
Improved	2 (15.4%)	4 (36.3%)	2
Unchanged	0	2	0
Aggravation	0	0	1

$p < 0.005$.

Table 4. *Outcome in patients with medically intractable seizures*

Case	Medication duration	Sz* type	Outcome	Obliteration	F/U duration	Sz free interval
1	1	C.P	free	complete	54	18
2	1.5	C.P	free	–	10	2
3	3	G.T.C	free	complete	77	27
4	10	G.T.C	free	complete	100	32
5	13	G.T.C	free	complete	43	17
6	29	F.M.S	free	partial	54	32
7	4	G.T.C	free	complete	48	20
8	10	G.T.C	free	partial	60	34
9	20	G.T.C	improved	partial	48	24
10	20	G.T.C	improved	complete	146	45
11	2	G.T.C	improved	complete	84	38
12	0.5	G.T.C	improved	partial	57	34
13	10	G.T.C	improved	–	72	20
14	6	G.T.C	unchanged	–	36	–
15	7	G.T.C	unchanged	partial	27	–

* *Sz* Seizure.

without antiepileptic medication. Of these 23 patients, 3 patients were seizure-free without receiving an anticonvulsant drug. The others continued to have medication during follow-up; slow drug withdrawal was then offered if they were seizure-free for 2 years. Ten (23.5%) patients were classed as ''seizure improved'' (at least one attack within the final year of follow up) and had a significant improvement in their seizures. One patient stopped taking the medication due to pregnancy. Eight (18.6%) patients were unchanged in seizure control. Two (4.6%) patients experienced aggravated seizures after radiosurgery (Table 2).

Of 26 patients who underwent cerebral angiographic follow up over 2 years after radiosurgery, complete obliteration of the AVM was confirmed in 13 patients and 11 (84.6%) of them remained seizure-free at the time of final evaluation. In 10 patients, the AVMs were partially obliterated and 2 (36.3%) of these patients were seizure-free. Two patients showed no change in their AVMs and neither was seizure-free. Overall, 26 patients remained available for analysis for 2 years of follow up. Fifteen patients were seizure-free and 6 patients had significant improvement of seizure control. This result suggest that patients with angiographical obliteration tend to be associated with higher seizure-free rates than those who remained nidus (84.6% vs. 36.6%, $p<0.005$) (Table 3).

Fifteen patients had experienced intractable seizure before radiosurgery and all 15 patients had frequent seizures despite anticonvulsant treatment. Medication duration ranged from 6 months to 20 years (mean 9.1 years). Follow up duration was from 27 to 146 months (mean 61.1 months). Table 4 shows the clinical characteristics of the patients and their response to radiosurgery. After radiosurgery, the seizures disappeared in 8 patients. Seizure frequently decreased in 5 patients and 2 patients was unchanged but no one experienced aggravated seizures. Five (71%) of 7 patients with complete obliteration were seizure-free and 2 (40%) of 5 patients with partial obliteration were seizure-free.

Other factors influencing seizure control are nidus volume, seizure frequency, and seizure duration. The lesser the volume, frequency, and duration was small, prognosis was the better. But there was no significant statistical difference.

There was no operative death among the 43 patients. Four (8.8%) patients experienced bleeding after GKRS, 2 patients had symptomatic ARE. Seizure was aggravated in 2 patients.

Discussion

The cause of epileptogenesis from cerebral AVMs is still unclear. A number of different hypotheses have been outlined by previous authors [15, 17, 31] including 1) focal cerebral ischemia attributable to a ''steal'' phenomenon resulting from a neighboring arteriovenous shunt; 2) gliosis, neuronal degradation, demyelination, and hemosiderin deposits lining the AVM bed; and 3) secondary epileptogenesis at a distance site ''kindling'' phenomenon, in which epileptic discharges are enhanced by an excitatory synaptic connection from the AVM.

Previously published surgical series reported a varying rate of success in improving seizure after the surgical excision of AVMs [3, 6, 14, 20, 22, 23, 31]. Currently, relatively good seizure results have been noted with

radiosurgical treatment of AVMs [4, 10, 13, 16]. New-onset seizure can be a complication of radiosurgery. However, in a multicenter analysis of complications following neurosurgical AVM treatment, 22 of 1255 (1.8%) patients experienced new or worsened seizures [8].

Some authors think that radiosurgery has a beneficial effect on seizure outcomes even before an AVM's complete obliteration [4, 10, 13, 16], although higher seizure-free rates were observed for patients with complete obliteration [4, 16]. One possible explanation is that irradiation might affect epileptogenesis from tissue surrounding the AVM, independent of radiation-induced AVM thrombosis [10, 13]. Others think that radiosurgical reduction of the steal phenomenon contributes to the resolution of epileptogenic activity from the surrounding ischemic area [10, 13, 16].

Several authors have suggested that seizures associated with AVMs are easy to control and that surgery allows good control of seizures [12, 14, 23, 26, 28, 31, 32]. Trumpy and Eldevik [28] cured 50% of their patients with preoperative seizure due to AVMs. Guidetti and Delitala [12] reported that seizures improved in 53% of patients after AVM surgery. Heros *et al.* [14] reported that over half of all preoperative seizures were cured or greatly improved after the resection of AVMs, and that only 12.7% worsened. However, several studies disclosed that epileptogenic foci secondary to AVMs become progressively more intractable [8, 9], or that surgery cannot contribute to seizure control [2, 3, 6, 20, 22]. Forster *et al.* [6] reported that only 4% of patients with epileptogenic AVMs were seizure-free after surgery. Parkinson and Bechers [22] stated that patients with preoperative seizures were likely to have them postoperatively. Drake [27] concluded that the excision of the AVM alone would not relieve associated epilepsy. The reported risk of new epilepsy after AVM surgery also varies, ranging from <10 to $>50\%$ [1, 3, 6, 14, 20, 28, 30].

Although the primary aim of radiosurgery for cerebral AVMs is to obliterate the nidus and eliminate the risk of bleeding, a positive effect of radiosurgery for seizure control has also been reported by several articles [18, 24, 27]. Steiner *et al.* [27] reported that 40 of 59 patients with seizure became seizure-free or were significantly improved after radiosurgery. In their series, 11 patients with medically intractable seizures became seizure-free with or without complete obliteration. Lunsford *et al.* [18] noted that 51% of 43 patients showed improved seizure control, and only one showed deterioration. These reports suggest that a focused single high dose of irradiation does have some beneficial effect on seizure related to AVMs in a high proportion of cases. But the effect of irradiation has not been quantified because of the complexity of the variables affecting seizure control, such as medication, presence or absence of previous hemorrhage or surgery, and physiological factors.

In our study, we suggest that Gamma Knife radiosurgery is a potentially valuable treatment modality for medically intractable seizure and provides some basis for a hemodynamic effect related to seizure control. Indeed, ischemia of the surrounding brain is considered to be one of the pathophysiological factors of epilepsy, and amelioration of the arteriovenous shunt should be expected to alter regional blood flow resulting in relief of epilepsy.

Conclusion

Our study provides evidence that Gamma Knife radiosurgery can improve symptomatic epilepsy associated with AVMs in a high proportion of treated patients and it provides some basis for the hemodynamic effect of radiosurgery on seizure associated with AVMs. Although we acknowledge that radiosurgery to intractable seizure has the effectiveness, because the number of cases was small, more investigation is needed.

References

1. Brown RD Jr, Wiebers DO, Forbes G, *et al* (1998) The natural history of ruptured intracranial arteriovenous malformations. J Neurosurg 68: 352–357
2. Crawford PM, West CR, Chadwick DW, *et al* (1986) Arteriovenous malformation of the brain: natural history in unoperated patients. J Neurol Neurosurg Psychiatry 49: 1–10
3. Crawford PM, West CR, Shaw MD, *et al* (1986) Cerebral arteriovenous malformation and epilepsy: factors in the development epilepsy. Epilepsia 27: 270–275
4. Eisenschenk S, Glimore RL, Friedman WA, *et al* (1998) The effect of LINAC stereotactic radiosurgery on epilepsy associated with arteriovenous malformations. Stereotactic Funct Neurosurg 71: 51–61
5. Engel J Jr (1987) Outcome with respect to epileptic seizures. In: Engel J Jr (ed) Surgical treatment of the epilepsies. Raven Press, New York, pp 553–571
6. Forster DMC, Steiner L, Håkanson S (1972) Arteriovenous malformation of the brain. A long-term clinical study. Neurosurg 37: 562–570
7. Fults D, Kelly DL Jr (1984) Natural history of arteriovenous malformation of the brain, A clinical study. Neurosurgery 15: 658–662
8. Garretson HD (1985) Intracranial arteriovenous malformations. In: Wilkins RH, Rengachary SS (eds) Neurosurgery. McGraw-Hill, New York, pp 1448–1458
9. Okabe T, Meyer JS, Okayasu H, *et al* (1983) Xenon-enhanced CT CBF measurement in cerebral AVMs before and after excision: contribution to pathogenesis and treatment. J Neurosurg 59: 21–31
10. Gerszten PC, Adelson PD, Kondziolka D, *et al* (1996) Seizure outcome in children treated for arteriovenous malformation using gamma knife radiosurgery. Pediatr Neurosurg 24: 139–144

11. Graf Ccj, Perret GE, Toner JC (1983) Bleeding from cerebral arteriovenous malformations as part of their natural history. J Neurosurg 58: 331–337
12. Guidetti B, Delitala A (1980) Intracranial arteriovenous malformation: conservative or surgical treatment. J Neurosurg 53: 149–152
13. Heikkinen ER, Konnov B, Melnikov L, *et al* (1989) Relief of epilepsy by radiosurgery of cerebral arteriovenous malformations. Stereotact Funct Neurosurg 53: 157–166
14. Heros RC, Korosue K, Diebold PM (1990) Surgical excision of cerebral arteriovenous malformation: late result. Neurosurgery 26: 570–578
15. Kraemer D, Award IA (1994) Vascular malformation and epilepsy: clinical consideration and basic mechanisms. Epilepsia 35 [Suppl] 6: S30–S34
16. Kurita J, Kawamoto S, Suzuki I, *et al* (1998) Control of epilepsy associated with cerebral arteriovenous malformations after radiosurgery. J Neurol Neurosurg Psychiatry 65: 648–655
17. Leblanc R, Feindel W, Ethier R (1983) Epilepsy from cerebral arteriovenous malformations. Can J Neurol Sci 10: 91–95
18. Lunsford LD, Kondzziolka D, Flickinger JC, *et al* (1991) Stereotactic radiosurgery for arteriovenous malformations of the brain. J Neurosurg 75: 512–524
19. Michelsen WJ (1979) Natural history of pathophysiology of arteriovenous malformations. Clin Neurosurg 26: 307–313
20. Murphy MJ (1985) Long term follow up seizure associated with cerebral arteriovenous malformations. Result of theraphy. Arch Neurol 42: 477–479
21. Ondra SL, Troupp H, George ED, *et al* (1990) The natural history of symptomatic arteriovenous malformations of the brain: a 24-year follow up assessment. J Neurosurg 73: 387–391
22. Parkinson D, Bachers G (1980) Arteriovenous malformations. Summary of 100 consecutive supratentorial cases. J Neurosurg 53: 285–299
23. Piepgras DG, Sundt TM Jr, Ragoowansi AT, *et al* (1990) Seizure outcome in patients with surgically treated cerebral arteriovenous malformations. J Neurosurg 78: 5–11
24. Pollock BE, Gorman DA, Schomberg PJ, *et al* (1999) The Mayo Clinic gamma knife experience: indication and initial result. Mayo Clinic Proc 74: 5–13
25. Pool JL (1962) Treatment of arteriovenous malformations of cerebral hemispheres. J Neurosurg 16: 136–141
26. Rasmussen T (1975) Surgery of epilepsy associated with brain tumors. In: Purpura DP, Perry JK, Walker RD *et al* (eds) Advances in neurology, vol 8. Neurosurgical management of epilepsies. Raven Press, New York, pp 227–229
27. Steiner L, Lindquist C, Adler J, *et al* (1992) Clinical outcome of radiosurgery for cerebral arteriovenous malformations. J Neurosurg 77: 1–8
28. Trumpy JH, Eldevik P (1977) Intracranial arteriovenous malformations: conservative or surgical treatment? Surg Neurol 8: 171–175
29. Turjman F, Massoud TF, Sayre JW, *et al* (1995) Epilepsy associated with cerebral arteriovenous malformations: a multivariate analysis of angioarchitectual characteristics. AJNR Am J Neroradiol 16: 345–350
30. Wilkins RH (1985) Natural history of intracranial arteriovenous malformations. A review. Neurosurgery 16: 421–430
31. Yeh HS, Kasiwagi S, Tew JM Jr, *et al* (1990) Surgical management of epilepsy associated with cerebral arteriovenous malformations. J Neurosurg 72: 216–223
32. Yeh HS, Tew JM Jr, Gartner M (1993) Seizure control after surgery on cerebral arteriovenous malformation. J Neurosurg 17: 12–18

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Surgical resection of cavernous angiomas located in eloquent areas – clinical research

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Summary

Background. In patients with lesions at the eloquent areas, the aim of surgical interventions should be a more radical removal of the lesions with preservation of brain function. In this retrospective study, our techniques for localizing lesion and the postoperative results of 26 patients with cavernous angiomas (CA) located at the eloquent areas are summarized.

Method. The MR based 3D-rendering images were reconstructed from the 2D MR images by using a computerized program. These images were obtained in all patients for the localization of their lesion. Following craniotomy, to verify the actual location of lesions, we compared the 3D-image to the exposed cortical surface. Simultaneously, intraoperative ultrasonogram (IOUS) was used for the accurate localization of the lesion. In order to minimize the damage to the eloquent area, the minimal corticotomy was planned at the margin of the sulcus nearest to the lesion.

Findings. An accurate localization of the lesion was possible in all 26 patients and the eloquent areas near the lesions were identified on the operation field. Complete removal of the CAs was done in all cases. One patient developed temporary monoparesis postoperatively, but the patient fully recovered in a month. Fourteen patients presented with preoperative seizures, and all patients had excellent seizure outcome after their surgery. The mean duration of the follow-up period was 27 months.

Conclusions. We could localize the lesion accurately using MRI 3D-rendering images and IOUS during the operation for CA. We planned minimal corticotomy to the lesion and we completely removed the lesion without causing any additional neurological deficit. Although CA can be located in eloquent areas, surgical removal of these lesions is a safe and effective treatment option for lowering the risk of developing symptoms and controlling the seizure.

Keywords: Cavernous angiomas; eloquent brain areas; minimal corticotomy.

Introduction

Cerebrovascular malformations are developmental abnormalities that affect the blood vessels supplying the brain. The most commonly used classification scheme subdivides these lesions into four categories: (1) venous malformations, (2) arteriovenous malformations, (3) cavernous malformations and (4) telangiectases. Although CAs constitute only 5–10% of cerebrovascular malformations, they are being increasingly recognized as a cause of seizures and focal neurological deficits [3, 7, 12]. Postmortem studies suggest that CA affect approximately 0.4–0.9% of the general population and 64–84% of CAs are located above the tentorium [3, 7, 9, 13]. Patients with supratentorial CA often present with epileptic seizures, and they less frequently present with intracranial haemorrhage or focal neurological deficits that are caused by the mass effect. However, with the introduction and advancement of MR imaging techniques for the diagnostic evaluation of CA, the number of diagnosed cases has risen dramatically for asymptomatic patients or for those patients suffering with nonspecific symptoms [11–13]. A general consensus exists that surgically removing CAs is appropriate for those patients with intractable epilepsy or progressive neurologic deficit due to CA's acute haemorrhage or mass effect. But controversy is going on with regard to treatment of those asymptomatic patients with incidentally found CAs, for patients with new-onset of seizure and patients with long lasting rare seizures [2, 9, 14]. Especially when CAs are located in eloquent brain areas, the possibility of postoperative morbidity and haemorrhage as sequela should be considered. Thus, the clinical outcome of surgery for these lesions has been a matter of concern.

In this study, we described our technique of surgical approach for CA in eloquent brain area and we report on the clinical results.

Patients and method

Patients

Between 2001 and 2005, 55 patients were operated in our department for resection of CA and their lesions were pathologically confirmed. Of these patients 26 with the following conditions were selected: 1) Patients with solitary lesion located in eloquent brain area, 2) when urgent surgical interventions were not required at the time of diagnosis and CA were found incidentally; we included patients with non-specific symptoms such as headache or dizziness without increased intracranial pressure and patients with new-onset seizure or long lasting rare seizures. Mean age of patients was 35 years old (19–59 years). Seventeen were male and 9 female. The medical records and MRI images were reviewed retrospectively, and average follow-up period was 27 months.

Localization of the lesion

MRI-based 3D-rendering images were obtained for all patients for localization of the lesion. The 3D-rendering images were reconstructed from the 2D MR images, upon which the lesion was drawn. They provided us with anatomical information about the location of the lesion and the gyri and sulci adjacent to the lesions in the eloquent brain area. This information was used for the preoperative planning and for performing the surgical procedures. To verify the actual location and to adjust the trajectory of dissection toward the lesion, we compared the 3D-rendering images to the exposed cortical surface. Functional MRI was done in 13 patients preoperatively to reveal the anatomical relationship between the lesions and the eloquent brain area. In 14 patients with the lesion located in the primary motor cortex area, the somatosensory evoked potential (SSEP) was done to identify the central sulcus.

By inspection and palpation, we identified the discoloration of the superficial CAs that were bleeding. Also, lesions exhibiting an abnormal consistency could be palpated. In 6 out of 26 cases, corticotomy was planned by this simple method. Intraoperative ultrasound (IOUS) was done for accurate localization of the lesion in the other 20 cases. On an ultrasound study, CAs generally appear as hyperechoic, mostly well demarcated lesions when using the bright-mode/grey-scale. Following craniotomy, the sterilely draped microprobe was placed on the dura with aseptic saline used as a coupling medium. After accessing the

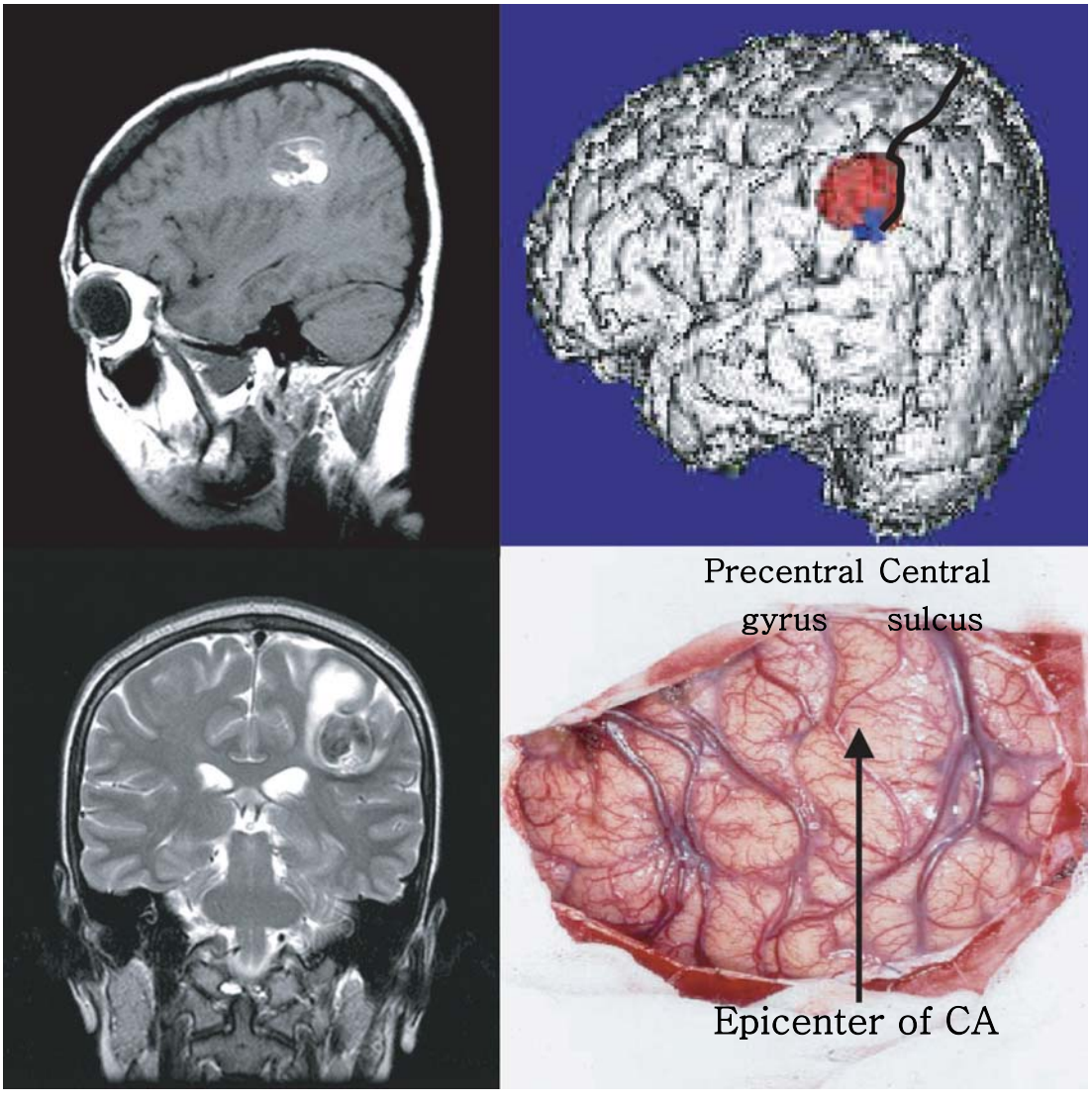

Fig. 1. (*Left*) T1 sagittal and T2 coronal MR images showing the subcortical CA in left precentral gyrus. (*Right*) Created MR 3D-rendering image showing the lesion and adjacent cortical anatomy. We could identify the epicenter of CA by comparing the operation field with 3D-rendering image

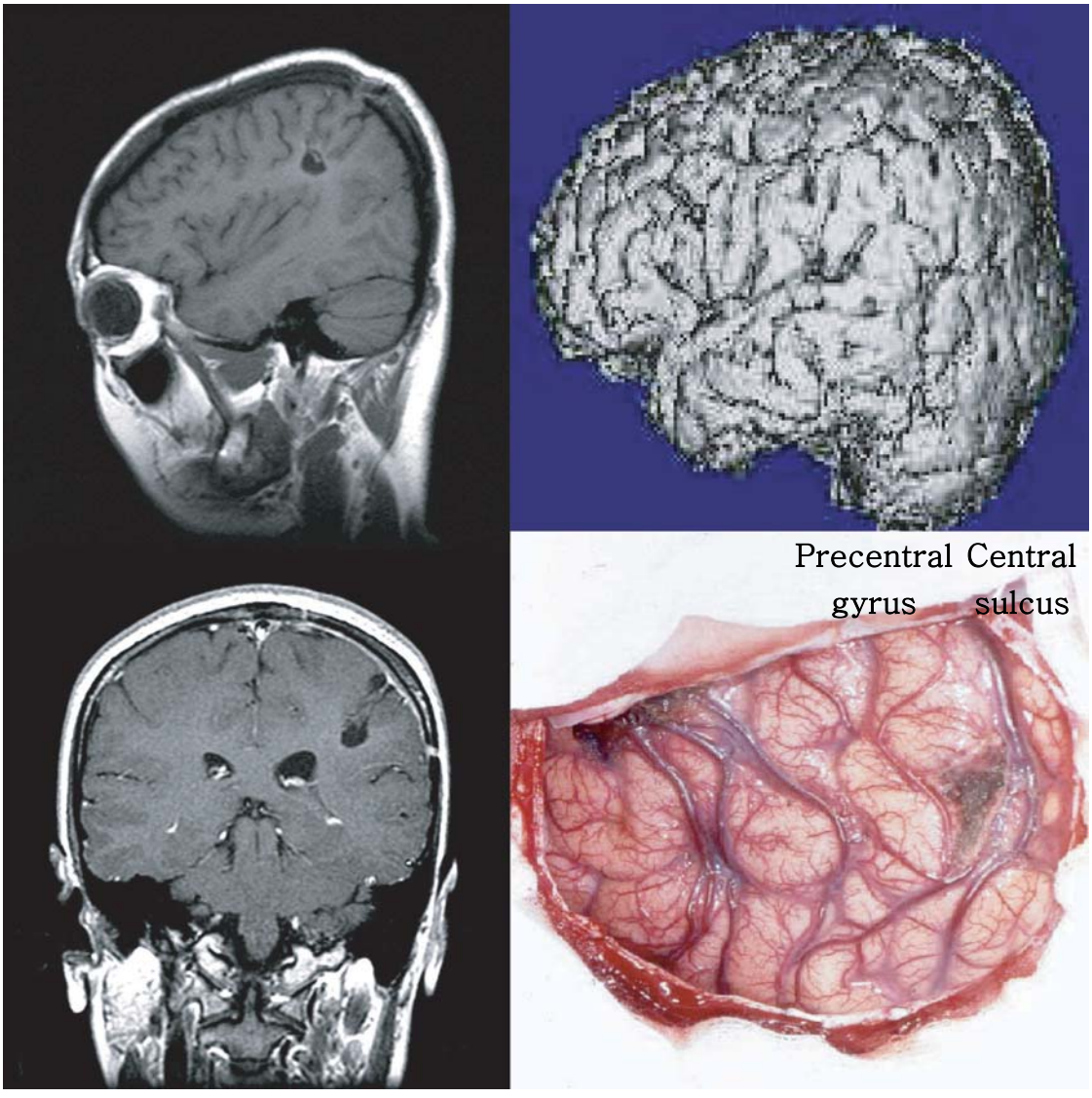

Fig. 2. (*Left*) T1 sagittal and coronal MR images showing the complete removal of CA. (*Right*) In order to minimize the damage of the precentral gyrus, corticotomy was performed at the margin of the central sulcus that was nearest to the lesion

anatomical orientation by using a frequency of 5–6 MHz, the frequency was raised to 8–9 MHz to evaluate the exact margin of the lesion. After opening the dura, the angioarchitecture of the overlying cortical surface was inspected and the best point for performing a corticotomy was chosen depending on sonographic information such as the vascular anatomy and the shortest distance to the lesion. Additionally, the examination could be repeated several times during the surgical resection, and this was also helpful for detecting the remaining lesion.

Surgical planning and procedure

The craniotomy site was determined using the 3D-rendering images that were taken preoperatively. Skin incision and osteoplastic craniotomy were done to expose the lesion and the eloquent brain area. After a craniotomy flap has been created and the dura opened, the anatomy of the sulci and gyri were identified by comparing the operation field with the 3D-rendering images (Fig. 1). Careful physical examination and IOUS helped to map the epicenter of the lesion. In order to minimize the damage of the gyri in the eloquent brain area, corticotomy was planned for the margin of the sulcus that was nearest to the lesion (Fig. 2). CAs have a low bleeding tendency and they are composed of haemosiderin and gliotic tissue that forms precise margins; thus, minimal corticotomy could almost always be performed. The CA and surrounding gliotic tissue were removed with care being taken to minimize the traction induced upon the eloquent brain area. Then, cranioplasty and wound closure were done by the standard neurosurgical technique.

Results

The location of the CA was in the primary motor cortex in 14 cases, the speech related cortex in 8 cases, the primary visual cortex in 3 cases and the basal ganglia in 1 case. The lesions varied in diameter from 5 to 40 mm (mean: 21 mm). The clinical characteristics at

Table 1. *Clinical manifestations of 26 patients with CA in eloquent brain areas*

Factors	No. of cases (%)
Presenting symptoms	
– Asymptomatic or incidentally discovered lesion	6 (23)
– Non-specific symptoms without IICP	6 (23)
– New-onset seizures	5 (20)
– Long-lasting rare seizures	9 (34)
Location of lesions	
– Primary motor cortex	14 (54)
– Speech related cortex	8 (30)
– Visual cortex	3 (12)
– Basal ganglia	1 (4)

IICP Increased intracranial pressure.

the time of diagnosis are presented in Table 1. On the preoperative MRI images, overt bleeding was found in 6 cases and microhaemorrhage was found in 15 cases, and this microhaemorrhage was accompanied by mass effect in 5 cases.

Accurate localization of the lesion was possible in all 26 patients and the eloquent brain area near the lesions was identified on the operation field. Complete removal of CAs was done in all cases. One patient developed temporary monoparesis in the upper extremities, but the patient fully recovered in a month. Acute complications related to the operation did not occur, though delayed sensory aphasia developed one week after an operation in one patient. The patient had developed haemorrhagic infarction in the left parietal lobe after removal of a subcortical CA in the left primary motor cortex, but the patient fully recovered without neurologic sequelae by instituting conservative management.

Of the 6 patients with non-specific symptoms such as headache and dizziness before their operations, the symptoms improved in 5 patients and they were unchanged in 1 patient postoperatively. Five patients with new-onset seizure became seizure-free postoperatively without taking any anti-epileptic drugs (AED). Nine patients with rare seizures also remained seizure-free, of whom 3 are on AED medication. The mean duration of follow-up was 29 months (6–54 months) for the 14 patients who had suffered preoperative seizure.

Discussion

CA constitutes 5–10% of all cerebrovascular malformations and the studies that have been conducted based on autopsy and MRI have suggested that CA affects approximately 0.4–0.9% of the general population. CA is most prevalent in the second to fourth decade of life and there is no gender difference in its prevalence [3, 7, 12, 13].

The presenting symptoms are due to haemorrhage and the mass effect of CA, and these vary widely from asymptomatic to non-specific symptoms, seizure and acute or progressive neurologic deficit. The CA below the tentorium frequently presents with focal neurologic abnormalities. On the other hand, CA above the tentorium often presents with seizure [1, 10, 11]. With the advancement of MR imaging techniques, the number of diagnosed cases has dramatically risen in asymptomatic patients. Previous studies have reported that 11–44% of patients with CA are asymptomatic [11–13].

The indications for surgical resection are different for each of the clinically presenting manifestations and the indications are influenced by other factors such as patient's age and gender, the location of the lesion and the multiplicity of the lesions. There is a general consensus that surgical resection of solitary CA is the treatment of choice for patients with progressive neurological deficit or medically intractable epilepsy. However, conservative management or surgical resection for the overall group of CAs is still a subject of intense controversy [2, 9, 14].

The CA patients with no history of clinical haemorrhage have an annual bleed rate of 0.7–4.2% [10, 13]. A first haemorrhage from a CA is rarely life threatening, but it may result in significant morbidity from which the patient may or may not fully recover. Particularly, the lesions in or near the functional cortex may exhibit overt neurological deficits after even minor bleeding.

The risk/benefit considerations of intervention for the patients with lesion located in the critical areas are more difficult. Although the surgical approach is associated with risk, the consequences of haemorrhage are more serious; hence, the potential benefit of lesion excision is also greater. In addition, the physiological burden of knowing that patients have a lesion needs to be considered. Frequent headache or slight non-specific symptoms can cause patients great anxiety, necessitating frequent clinical evaluation and imaging studies. A modern surgical series revealed that solitary supratentorial CA can be resected with few complications and no death beyond the standard risks of general anesthesia [2, 4, 5, 15, 18]. These series emphasized that accurate localization of the lesions must be done for minimizing the surgical trauma to the adjacent functional cortex.

To reduce perioperative morbidity and mortality, the neurosurgeon has a broad spectrum of localization and

navigation devices such as intraoperative CT, intraoperative MRI and the frameless neuronavigation system. Before the computer-assisted surgery era, the resection of lesions located in the functional cortex presented with a high risk of morbidity and mortality. This was probably due to performing large corticectomies in order to find the lesions. Wadley *et al.* reported that after routine use of preoperative CT scan and localization by using skin markers, the results became better with morbidity ranging from 20 to 40% and with a mortality rate ranging from 0 to 20% [16]. Gralla *et al.* used MRI neuronavigation in combination with intraoperative MR technique for operations on 26 patients with solitary CA; they observed a deterioration of neurological function in only 3.8% of patients [4]. However, for the application of MRI neuronavigation, it takes a long time to prepare for the operation, and changed location of the lesion during surgery due to leakage of cerebrospinal fluid must be considered. 3D-rendering images can readily be reconstructed from the preoperative MRI without performing additional imaging studies. By comparing the operation field to the 3D-rendering images, it is possible to accurately localize the lesion. In our study, we could identify the precise location of the lesion in the operation field by using the 3D-rendering images in all 26 cases, and we could plan the minimally necessary corticotomy for approaching the lesion.

IOUS has been used by neurosurgeons for about 50 years and numerous reports have revealed the availability of this technique [6, 8, 15, 18]. Lunardi and Acqui suggested that IOUS is superior to MRI navigation for localizing lesions because IOUS is a real-time imaging technique and it is not influenced by changed location of the lesion during surgery [8]. Woydt *et al.* compared IOUS and intraoperative MRI for operating CAs, and they reported that although both modalities help to accurately localize the lesion, IOUS is superior to MRI navigation because IOUS is applicable in all surgical positions, it gives information about local blood flow and it can be applied several times during the operation [17]. In our study, the sonographical orientation and localization at the cortical surface guided the neurosurgeon directly to the target in 20 cases. As a real time method, it is suggested that IOUS is an accurate and technically reliable method for localization of CA.

Seizures are the most common manifestation of supratentorial CAs, and they account for 40–80% of the presenting symptoms [3, 7, 13]. Previous studies have suggested that epilepsy secondary to CA could be the result of either haemosiderin interstitial deposition or the formation of cortical scars. One prospective study by Moriarity *et al.*, showed that a supratentorial CA was associated with an estimated 2.4%/year cumulative risk of new seizures [10]. It is known that seizure in CA patients is not easily controlled with AED treatment, and Robinson *et al.* reported that the response to the drugs was gradually decreased when only medical treatment was done [13]. A recent study reported that for patients with solitary CA, seizure was controlled in 78–88% of the patients postoperatively, and the duration and frequency of preoperative seizure were the most important prognostic factors [1, 19]. Despite that patients with intractable seizures were excluded from our study, the fact that 14 patients with preoperative seizure became seizure-free implicates that surgical removal of the CA is very effective for controlling seizure. However, for the 9 patients in our study with preoperative rare seizures, further observation and evaluation is being done.

Conclusions

We were able to localize the lesion accurately by using MRI 3D-rendering images and IOUS during operations for CA. Furthermore, we could obtain the necessary anatomical information concerning the adjacent eloquent brain area. We planned minimal corticotomy to the lesions and safely removed the lesions, even in the eloquent brain area, without producing neurological deficits. In conclusion, for patients with no symptoms or for those with rare seizures, surgical removal of CA is a safe and effective treatment option for lowering the risk of developing symptoms and for controlling seizure.

References

1. Casazza M, Broggi G, Franzini A, Avanzini G, Spreafico R, Bracchi M (1996) Supratentorial cavernous angioma and epileptic seizures: preoperative course and postoperative outcome. Neurosurgery 39: 26–34
2. Conrad M, Schonauer C, Morel Ch, Pelissou-Guyotat I, Deruty R (2002) Computer-assisted resection of supra-tentorial cavernous malformation. Minim Invas Neurosurg 45: 87–90
3. Curling OD Jr, Kelly DL, Elster AD, Craven TE (1991) An analysis of the natural history of cavernous angiomas, J Neurosurg 75: 702–708
4. Gralla J, Granslandt O, Kober H, Buchfelder M, Fahlbusch R, Nimsky C (2003) Image-guided removal of supratentorial cavernomas in critical brain areas: application of neuronavigation and intraoperative magnetic resonance imaging. Minim Invas Neurosurg 46: 72–77
5. Gumprecht H, Ebel GK, Auer DP, Lumenta CB (2002) Neuronavigation and functional MRI for surgery in patients with lesion in eloquent brain areas. Minim Invas Neurosurg 45: 151–153

6. Hata N, Dohi T, Iseki H, Takakura K (1997) Development of a frameless and armless stereotactic neuronavigation system with ultrasonographic registration. Neurosurgery 41: 608–614
7. Kim DS, Park YG, Choi JU, Chung SS, Lee KC (1997) An analysis of the natural history of cavernous malformations. Surg Neurol 48: 9–18
8. Lunardi P, Acqui M (1993) The echo-guided removal of cerebral cavernous angiomas. Acta Neurochir (Wien) 123: 113–117
9. Maraire JN, Awad IA (1995) Intracranial cavernous malformations: lesion behavior and management strategies. Neurosurgery 37: 591–605
10. Moriarity J, Clatterbuck R, Rigamonti D (1999) The natural history cavernous malformations. Neurosurg Clin N Am 10: 411–417
11. Requena I, Arias M, Lopez-Ibor L (1991) Cavernomas of the central nervous system: clinical and neuroimaging manifestation in 47 patients. J Neurol Neurosurg Psychiatry 54: 590–594
12. Rigamonti D, Hadley M, Drayer BP, Johnson PC, Hoenig-Rigamonti K, Knight JT, Spetzler RF (1988) Cerebral cavernous malformations: incidence and familial occurrence. N Engl J Med 319: 343–347
13. Robinson JR, Awad IA, Little JR (1991) Natural history of cavernous angioma. J Neurosurg 75: 709–714
14. Robinson JR, Awad IA, Magdinec M, Paranandi L (1993) Factor predisposing to clinical disability in patients with cavernous malformations of the brain. Neurosurgery 32: 730–735
15. Tirakotai W, Sure U, Benes L, Boris K, Bien S, Bertalanffy H (2003) Image-guided transsylvian, transinsular approach for insular cavernous angiomas. Neurosurgery 53: 1299–1305
16. Wadley J, Dorward N, Kitchen N, Thomas D (1999) Preoperative planning and intra-operative guidance in modern neurosurgery: a review of 300 cases. Ann R Coll Surg Elgl 81: 217–225
17. Woydt M, Horowski A, Krone A, Soerensen N, Roosen K (1999) Localization and characterization of intracerebral cavernous angiomas by intra-operative high resolution colour-duplex-sonography. Acta Neurochir (Wien) 141: 143–152
18. Woydt M, Krone A, Soerensen N, Roosen K (2001) Ultrasound-guided neuronavigation of deep-seated cavernous haemangiomas: clinical results and navigation techniques. Br J Neurosurg 15: 485–495
19. Zevgaridis D, van Velthoven V, Ebeling U, Reulen HJ (1996) Seizure control following surgery in supratentorial cavernous malformations: a retrospective study in 77 patients. Acta Neurochir (Wien) 138: 672–677

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Spinal cord

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Spinal cord stimulation and cerebral haemodynamics

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Summary

After the demonstration that spinal cord stimulation (SCS) can improve peripheral blood flow it was Hosobuchi ('86) who first studied the effect of SCS on cerebral blood flow (CBF) in human beings. Our group found that SCS can produce either an increase of CBF or a reduction or no effect. In patients studied with both SPECT technique and TCD, the sign of the induced variations, when present in both, was the same. Cervical stimulation produces more frequently an increase in CBF (61% of cervical stimulations). Our experimental studies confirm that SCS and CO_2 interact with the mechanism of regulation of CBF in a competitive way and produce a reversible functional sympathectomy. Further experimental reports suggest that SCS 1) drastically prevents cerebral infarction progression in cats; 2) improves clinical symptoms of patients in persistent vegetative states; 3) suppress headache attacks in migraneous patients; 4) significantly reduces ischemic brain oedema in rats. Following these clinical and experimental observations, Hosobuchi first used cervical SCS for the treatment of cerebral ischemia in man ('91). More recently we confirmed the therapeutic effect of SCS on ischemic stroke in humans, experimental brain injury and cerebral vasospasm in rabbits.

Keywords: Spinal cord stimulation; cerebral blood flow; stroke; brain injury; vasospasm; cerebral autoregulation; functional sympathectomy.

SCS and CBF: historical data

SCS affects peripheral, coronaric and CBF in humans. Functional reversible sympathectomy may be one of the mechanisms put in play by SCS to produce such effects [19, 20, 25].

The possibility to interfere with the mechanisms of regulation of the cardiovascular system is quite fascinating.

After the demonstration that SCS can improve peripheral blood flow [19], Reis showed in 1984 a reduction in the intracranial vasomotor control together with an increase of the cerebral blood flow (CBF) following the electrical stimulation of the medullary reticular formation [24]. In 1985, Hosobuchi, one of the pioneers of modern neurostimulation, first observed the effect of SCS on CBF in human beings [6]. He studied by SPECT technique ten patients treated with SCS for chronic intractable pain, five had an electrode at the C3–C4 level, the remaining five had a T8–T9 electrode. The result of his study was that cervical stimulation was producing a significant rise in hemispheric CBF. This effect was ipsilateral to the induced paresthesia suggesting that the alteration in CBF was not related to the increased cerebral metabolic rate resulting from the afferent volley produced by the artificial stimulation of the spinal cord. Among the possible ways of assessing CBF in humans, transcranial Doppler sonography (TCD) was utilized as well according to the Aaslid criteria [1]. TCD allows a non-invasive evaluation of blood velocity within intracranial arteries [12, 13]. Since there is a significant positive correlation between blood velocity and CBF, we could study an extensive series of patients wearing spinal cord epidural electrodes at different segmental levels with both TCD and Xe technique in order to 1) confirm the effect of SCS on CBF; 2) compare observations made with two different methods; 3) evaluate the correlation between the stimulated spinal segmental level and the effect on CBF, and 4) evaluate the mechanism put in play by SCS in responsive patients [21, 22]. SCS can produce either an increase of CBF or a reduction or no effect. In patients studied with both Xe technique and TCD the sign of the induced variations, when present in both, was the same. A reduction of CBF is very rare and occurs for more caudal electrodes location (16% of thoracic SCS) while cervical stimulation produces more frequently an increase in CBF (61% of cervical stimulations). The stimulation of different cord levels in the same patient can produce different effects. The result of the stimulation in the same patient is always reproducible during time. Furthermore Mazzone, even

confirming such an observation with both xenon 133 inhalation technique and TCD, focused the attention of the concept of ''redistribution of CBF'' rather than an absolute change in CBF during SCS. Intriguingly he concluded that ''a symmetrical increase in regional CBF was found mainly in the anterior regions; frontal lobe functional activation by the ascending reticular pathways through the thalamo-cortical projections might be hypothesised'' [17, 18].

SCS and CBF: the study of the mechanisms

SCS interferes with the mechanisms of regulation of heart rate in man by means of so called ''reversible functional sympathectomy''. A functional reversible sympathectomy was advocated as a possible mechanism for SCS in man [20].

Linderoth demonstrated that SCS-induced peripheral vasodilatation was abolished by bilateral sympathectomy in rats and that peripheral sympathetic activity, recorded from the sympathetic chain close to the stellate ganglion, might be suppressed by SCS applied at the Th2 level in cats [12]. Further personal studies aimed to investigate on sympathetic balance during experimental SCS confirmed the functional reversible sympathectomy also in mediating CBF changes [26, 29]. CBF of the internal carotid arteries were measured in four rabbits by means of a Doppler device and an electromagnetic flowmeter (Transonic Mod. T 106, Ithaca, NY, USA) in basal conditions, during sympathetic trunk stimulation (STS) (10 volts, 10 cycle per sec, 0.5 msec duration, for 1 min) at the neck, during SCS (210 microsec duration, 80 cycle per sec, with intensity 2/3 of the motor threshold, applied for 20 min) and finally during simultaneous SCS and sympathetic trunk stimulation. A reduction of CBF was evident in every case soon after starting STS. At the end of stimulation the effect disappeared immediately. SCS produced an increase of CBF in rabbits, and no change in the remaining 2 animals. In 2 animals showing an increase of CBF during SCS, STS produced only 25–30% of its effect while in the remaining 2 animals vasoconstriction was comparable to the one observed in basal condition.

Data obtained showed that a decrease (65–70%) of cervical sympathetic excitability occurs as a consequence of SCS. In the same year Myklebust found norepinephrine levels markedly affected during SCS confirming a sympathetic inactivation secondary to neurostimulation [23] and Linderoth [13, 14] found out that SCS reduces ischemia in an animal model of limb vasospasm with a ''preventing'' effect. Among the possible factors involved, substance P (SP), vasoactive intestinal polypeptide (VIP) and calcitonin gene-related peptide (CGRP) have been discussed [14]. On the other hand Hosobuchi showed a persistent elevation of CBF after interruption of the stimulation, suggesting the involvement of humoral factors; in fact indomethacin partially blocked the effect of SCS on CBF in 2 patients, while atropine did not affect the results [6].

Personal studies aiming to better understand the possible vascular autoregulatory mechanisms involved were performed on the ocular flow changes during SCS [30]. Both ophthalmic and cerebral haemodynamics underlay similar autoregulatory mechanisms: 1) the brain and the retina are surrounded by biological fluid as cerebrospinal fluid and corpus vitreum; 2) perfusion pressures of both central nervous system and eye can be considered as the difference between arterial and endocavitary pressure; 3) constant CBF and OBF are provided by the same autoregulatory mechanisms (myogenic, metabolic, neurogenic) [30]. Middle cerebral artery blood flow velocity by TCD and pulsatile ocular blood flow (OBF) by means of the Langham System were evaluated at rest and during cervical SCS in a group of patients [11]. A strict parallelism between cerebral and ocular haemodynamic changes (a decrease, an increase and no changes) was shown in three patients wearing cervical and thoracic electrode during stimulation, leading to the discussion on the role of autoregulation, possible common target of SCS in mediating such an effect [30].

Further personal study on the possible mechanisms involved by cervical SCS in TCD assessed responsive patients was performed by using the CO_2 autoregulation test. This work was done in cooperation with the Department of Internal Medicine of our University [21, 28]. The TCD patterns were evaluated and compared during progressive hypercapnia, both in basal conditions and during SCS. Hypercapnia was induced by rebreathing a mixture containing, at the beginning of the rebreathing period, 7% CO_2 and 93% O_2. The CO_2 concentrations were continuously monitored by mass spectrometry. The variables of the respiratory model were evaluated by a pneumotachograph. As is well known, an increase in CO_2 produces a vasodilatation which is detected by TCD with an increase in blood velocity and a decrease in resistance parameters [28]. By repeating the same study in the same patients during SCS we found a reduction of the response to CO_2. A possible explanation of such a phenomenon is that SCS and CO_2 interact with the mechanism of regulation of CBF in a competitive way.

They could act at the level of the same target and make it not amenable to other interference. If this is so, since the target of CO_2 are the preterminal arterioles, so called resistance arterioles, we could extrapolate that they are at least one of the target of SCS in producing its cerebrovascular effect. Finally, Isono found out that no haemodynamic effect occurs during SCS when the dorsal column is sectioned at the medullo-cervical junction thus confirming the role of specific spinal cord pathways in determining the increase of CBF during SCS [9, 10].

SCS and CBF: the experimental evidence

In 1987 Garcia-March reported CBF changes induced by SCS in animals [4] and in 1994 such evidence was confirmed by personal studies [26]. In the former study dogs were used to determine hemodynamic changes with electromagnetic flowmetry in the carotid territory, goats were used to evaluate hemispheric blood flow with the same technique and with 131 iodo antipyrine brain scintigraph. The results showed an average increase of CBF at the common and internal carotid level of more than 60% and an increase of CBF of more than 50%. These changes occurred during the first 15 minutes of stimulation [2]. In the latter study 23 New Zealand white rabbits were stimulated at cervical level and CBF detected by using CW Doppler and electromagnetic flowmeter. During SCS an increase in CBF was detected in 52.5% of the cases, a decrease in 19.5%, no change in 38%. Significant CBF Changes were evident from the 5th minute of SCS, the CBF changes ranging between 20 and 100% (mean 60%). Bilateral or monolateral changes were independent of the electrode site. One year later Isono confirmed by hydrogen clearance method an increase in CBF during cervical SCS in cats up to 140% lasting for 15 min after the end of SCS [20].

Possible terapeutical implications

Experimental

Interestingly, Matsui and Hosobuchi first studied the effects of SCS on experimental stroke [16]. They used a cat middle cerebral artery occlusion model (MCAO). Three groups were studied: a control group had only the occlusion of the middle cerebral artery, a sham operated had also the implantation of an epidural spinal electrode at the cervical level but no spinal stimulation, and a third group underwent cervical SCS (1–2 volts, 50 Hz) starting 6 hours after awakening from the operation. Mortality rate and infarct size in the three groups were analyzed.

Cervical SCS prolonged the survival rate within 24 hours after MCAO, compared to group 1 and 2, but there was no difference in total survival rate between groups 2 and 3.

The infarct size showed no difference in the dead cats of the three groups, but a significant difference occurred among the surviving cats of groups 2 and 3 demonstrating that cerebral SCS prevents the progression of brain infarction. The authors raised the question: ''is cervical SCS producing a luxury perfusion, potentially risky in acute infarction or does it help saving the penumbra zone of non functioning but still viable tissue that recovers its function as a consequence of improvement of blood flow?''. Only ''a useful effect on experimental stroke'' could be generically claimed. Three years later Gonzalez-Darder showed that cervical SCS significantly reduces brain oedema on diffuse cerebral oedema achieved by temporary occlusion of both carotid arteries followed by a reperfusion period [5]. Such a protection from ischemia induced oedema occurs when stimulation starts one hour before ischemia and just after ischemia. The mechanism mediating such effect of SCS could be a global increase of CBF limiting the extension and intensity of ischemia or metabolic changes in cerebral tissue protecting the brain against ischemia or the activation of systems changing the intracranial vascular response. In 1994 Broseta published the results of cervical SCS in three groups of different experimental stroke models in rabbits (1. bilateral carotid ligation, 2. unilateral microcoagulation of MCA and 3. microcoagulation of vertebral artery); SCS was performed one week after vessel obstruction. An improvement of CBF ranging from 27% up to 32% was recorded by Laser Doppler technique in the lesional area [2].

In 2001 personal studies were undertaken with the aim to evaluate the possible preventing effect of SCS in an animal model of combined ischemic and traumatic injury [36]. Twenty New Zealand rabbits underwent ligature of both carotid arteries and a right hemispheric craniectomy as well as about three hours' mechanical injury (200 mg) over the dura. In 10 animals (control group) SCS was not delivered; in 10 (SCS group) cervical SCS was started 20 min after arterial ligation and before the craniectomy and the mechanical injury. In two animals of both groups Near Infrared Spectroscopy (NIRS) was used; the probe was fixed over the dura during the whole experiment. Changes in deoxihemoglobine (HHb), oxihemoglobine (HbO_2) and citochrome

aa3 (Cit aa3) redox state were recorded on line [3]. MR examination was performed in all animals at the end of the experiments. Compared to the control group, none but one of the SCS showed lesional pattern far from the craniectomy suggesting a ''preventing'' effect of SCS on the secondary damage associated with our model of combined ischemic and traumatic brain injury; moreover NIRS showed changes consistent with CBF salvage in the craniectomy area. From 1994 to 2001 personal studies were performed on the effects of cSCS on experimental ≪early spasm≫ [31–34]. Based on the suggested role of the sympathetic system in mediating vasospasm, the possible interferences of SCS with the natural history of experimental so called ''early spasm'' was investigated. Such a short lasting phenomenon is very easy to be studied in the lab. Vasospasm due to SAH is both ''acute'' and ''recurrent''. Early spasm occurs within minutes of the SAH, its duration is approximately 1 hour. Twenty-nine adult Burgundy rabbits were studied. *Group 1*: under homeostatic monitoring, ''on-line'' carotid blood flow (carotid BF) changes produced by SAH in cisterna magna of 12 (plus 12 sham treated) animals were studied from the common carotid artery after external carotid artery occlusion before, during SAH up to the end of the experiments. All the animals underwent digital subtraction cerebral panangiography (CPA) after SAH obtaining a significant increase of carotid BF only when basilar vasospasm was shown by CPA. Carotid BF increase during basilar vasospasm was defined ''functional monitoring'' of early spasm. *Group 2*: twelve animals wearing a cervical epidural electrode underwent carotid BF ''functional monitoring'' of early basilar spasm before and during CSCS. Findings obtained were: carotid BF changes during cervical SCS occurred in 10 animals. No carotid BF changes (i.e. no basilar vasospasm) occurred after SAH up to the end of the experiments in all the stimulated animals. The role of reversible functional sympathectomy in mediating the effect of SCS on ''early spasm'' seemed able to prevent ≪early spasm≫ due to SAH in all animals studied, independent of occurrence and sign of stimulation induced CBF variations.

Clinical

Soon after some preliminary observations, there was great interest with regard to possible clinical applications. The first attempt was performed in 1989 by Kanno who reported 23 patients in vegetative states treated with SCS at the level of C2. A good clinical improvement was evident in eight. Regional CBF was evaluated by SPECT in 20 cases. A decrease as well as an increase of CBF was shown, but there was no a clear correlation with clinical outcome [8]. Changes in CBF following SCS in patients with impaired consciousness were also observed by Matsui *et al.* by using SPECT and Xe wash out technique. Again, although an increase in CBF was shown in some patients, there was no correlation with the clinical outcome [15]. The observations made in coma patients are complex to be analysed because of the variability of the clinical pattern, the extensive damage and the remarkable preexisting functional alterations. Following these clinical and experimental observations Hosobuchi first used cervical SCS for the treatment of cerebral ischemia [7]. For this purpose he selected 3 patients with symptomatic cerebral ischemia caused by advanced arteriosclerotic vascular disease or bilateral carotid occlusive disease non amenable to conventional surgery because ''of an unacceptably high surgical risk or because their symptoms were not severe enough to justify the risk of the procedure''. In all three cases, cervical SCS alleviated the symptoms of ischemia. Xenon-CBF studies or single-photon emission computer tomography showed increased CBF in response to cervical SCS. Hosobuchi's results seemed to justify further clinical trials.

In 1994, a personal experience was published concerning the case of a 64 year old patient who developed a severe spastic hemiparesis and dysphasia following a left parieto-temporal chronic ischemic stroke [27]. Clinical and neurophysiological study (surface polyelectromyography) were performed together with TCD examination before and after 7 days of SCS. An improvement of clinico-neurophysiological findings were observed as well as an increase of TCD CBF velocity (+43% right; +130% right). The evidence of an improvement of dysphasic disturbance suggested the main role of CBF changes, compared with the neurogenic enhancement, in mediating therapeutic effect of SCS [27]. In the same year Broseta published the results of SCS performed on 10 patients presenting with various cerebral low perfusion syndromes [2]. Though not constant, an increase of alertness, retention, speech, emotional lability and performance in skilled acts was achieved. No MRI changes were observed, though SPECT readings showed an ''increase in blood flow in the penumbral perilesional area''.

Finally personal conclusive results were published concerning 18 patients harbouring a TC/MRI cerebral lesional pattern dealing with a vascular injury (4 haemorrages; 14 ischemias. In this study a complex haemo-

dynamic assessment was performed by using TCD, SPECT and NIRS [35]. The findings were as follows.

SPECT group: an increase of regional CBF during SCS was measured far from the stroke areas in 9 patients, further decrease in CBF was found in 2, no changes in one. *TCD group*: an increase of CBF velocities during SCS was found in 4 patients, no changes in 6, a decrease in one. *NIRS group*: data consistent with and increase in CBF were obtained during SCS in the only patient that had undergone such a study. In 6 patients studied with different techniques, data obtained fitted only in two patients. In 3 patients no changes in TCD were faced with changes in SPECT. In one case an improvement in TCD was evident in the left while an improvement of SPECT was shown in the right side.

As matter of fact, according to the previous experiences of Mazzone, evidence of a redistribution of CBF more than a clear increase was shown in such patients [17, 18]. The personal conclusion that SCS is a valid therapeutic tool in stroke patient even if, as matter of fact, parallelism between clinical and haemodynamic changes during SCS was not demonstrated in our patients, raising the question on the role of ischemic penumbra in mediating clinical improvement, otherwise advocated by Broseta's previous experience in order to justify clinical improvement [2]. In his paper on the ⟨⟨treatment of cerebral ischemia with SCS⟩⟩ Hosobuchi concluded: . . .''although no mechanism clearly responsible for this intriguing therapeutic efficacy can be proposed yet, further clinical trials of SCS for inoperable cerebral ischaemia may be justified'' [7]. So far, as shown, data concerning an increase in local or global CBF in stroke as well as in low-perfused patients during SCS have been published, but no clear indications for SCS in stroke to merely improve CBF have been accepted.

In conclusion, there is clear evidence that SCS, particularly at the cervical level, affects the CBF, but further studies are needed before speculating on all the mechanisms mediating such an effect and its possible applications. Although all these results are quite exciting, there are still too many question marks to be answered prior to extending such observations into clinical practice. The literature data as well as personal observations seems to suggest a ''preventing'' rather than ''therapeutic'' effect of SCS on cerebrovascular diseases models in animals, as demonstrated for cerebral oedema, stroke and vasospasm.

Further experimental and clinical studies are required to confirm a ''preventing'' effect of SCS on the chronic phase of cerebral vasospasm in humans and to investigate on the ''therapeutic'' rather than ''preventing'' effect of SCS on cerebro-vascular diseases.

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References

1. Aaslid R, Markwalder TM, Nornes H (1982) Noninvasive transcranial Doppler ultrasound recording of flow velocity in basal cerebral arteries. J Neurosurg 57: 769–774
2. Broseta J, Garcia-Mark G, Sancez-Ledesma MJ, Goncalves J (1994) High cervical spinal cord electrical stimulation in brain low perfusion syndromes: experimental basis and preliminary clinical report. Stereotact Funct Neurosurg 62: 171–178
3. Colacino JK, Grubb B, Jobsis FF (1981) Infrared technique for cerebral blood flow: comparison with 133-xenon clearance. Neurol Res 3: 17–31
4. Garcia-March G, Sanchez-Ledesna MJ, Broseta J (1987) Effect of high cervical spinal cord stimulation on carotid and cerebral blood flow. An experimental study. Proceedings of the 8th European Congress of Neurosurgery, Barcelona, Spain, p 106
5. Gonzalez-Darder J, Canadas-Rodriguez D (1991) Effects of cervical spinal cord stimulation in experimental ischemic oedema. Neurol Res 13: 229–232
6. Hosobuchi Y (1985) Electrical stimulation of the cervical spinal cord increases cerebral blood flow in humans. Appl Neurophysiol 48: 372–376
7. Hosobuchi Y (1991) Treatment of cerebral ischemia with electrical stimulation of the cervical spinal cord. PACE 14: 122–126
8. Kanno T, Yoshifumi K, Yokoyama T, Shoda M, Tanji H, Nomura M (1989) Effects of dorsal column spinal cord stimulation on reversibility of neuronal function. Experience of treatment for vegetative states. PACE 12: 733–742
9. Isono M, Fukjiki M, Kaga A, Hori S (1989) Effect of spinal cord stimulation on cerebral blood flow. Proceedings of the X Meeting of World Society of Stereotactic and Functional Neurosurgery, Maebashi, Japan, p 136
10. Isono M, Kaga A, Fujiki M, Mori T, Hori S (1995) Effect of spinal cord stimulation on cerebral blood flow in cats. Stereotact Funct Neurosurg 64: 40–46
11. Langham ME, To'mey KF (1978) A clinical procedure for the measurement of the ocular pulse – pressure relationship and the ophthalmic arterial pressure. Acta Ophtalmol [Suppl] (191) 67: 17–25
12. Linderoth B, Gunasekera L, Meyerson BA (1991) Effects of symphathectomy on skin and muscle microcirculation during dorsal column stimulation. Animal studies. Neurosurgery 29: 874–879
13. Linderoth B, Gherardini G, Ren B, Lundeberg T (1995) Preemptive spinal cord stimulation reduces ischemia in an animal model of vasospasm. Neurosurgery 37(2): 266–271
14. Linderoth B, Gherardini G, Ren B, Lundeberg T (1995) Severe peripheral ischemia after vasospasm may be prevented by spinal cord stimulation. A preliminary report of study in a free flap animal model. Acta Neurochir [Suppl] 64: 101–105
15. Matsui T, Asano T, Takakura K, Yamada R, Hosobuchi Y (1989) Beneficial effects of cervical spinal cord stimulation on patients with impaired consciousness: a preliminary report. PACE 12: 718–725

16. Matsui T, Hosobuchi Y (1989) The effects of cervical spinal cord stimulation on experimental stroke. PACE 12: 726–732
17. Mazzone P, Pisani R, Nobili F, Arrigo A, Rosadini G (1995) Assessment of regional cerebral blood flow during spinal cord stimulation in humans. Stereotact Funct Neurosurg 64: 197–201
18. Mazzone P, Rodriguez G, Arrigo A, Nobili F, Rosadini G (1996) Cerebral haemodynamic changes induced by spinal cord stimulation in man. Ital J Neurol Sci 17: 55–57
19. Meglio M, Cioni B, Dal Lago A, De Santis M, Pola P, Serricchio M (1981) Pain control and improvement of peripheral blood flow following epidural spinal cord stimulation. Case report. J Neurosurg 54: 821–823
20. Meglio M, Cioni B, Rossi GF, Sandric S, Santarelli P (1986) Spinal cord stimulation affects the central mechanisms of regulation of heart rate. Appl Neurophysiol 49: 139–146
21. Meglio M, Cioni B, Visocchi M, Nobili F, Rodriguez G, Rosadini G, Chiappini F, Sandric S (1991) Spinal cord stimulation and cerebral haemodynamics. Acta Neurochir (Wien) 111: 43–48
22. Meglio M, Cioni B, Visocchi M (1991) Cerebral haemodynamics during spinal cord stimulation. PACE 14: 127–130
23. Myklebust JB, Cusick JF, Boerboom LE, Prieto TE, Khan TA (1995) Vascular effects of spinal cord stimulation in the monkey. Stereotact Funct Neurosurg 64: 32–39
24. Reis DJ (1984) Central neural control of cerebral circulation and metabolism, vol. 2. In: Mac Kenzie ET (ed), Raven Press, NY, pp 91–119
25. Sandric S, Meglio M, Bellocci F, Montenero AS, Scabbia E, D'Annunzio V (1984) Clinical and electrocardiographic improvement of hischaemic heart disease after spinal cord stimulation. Acta Neurochir [Suppl] 33: 543–546
26. Visocchi M, Cioni B, Vergari S, Marano G, Pentimalli L, Meglio M (1994) Spinal cord stimulation and cerebral blood flow: an experimental study. Stereotact Funct Neurosurg 62: 186–190
27. Visocchi M, Cioni B, Pentimalli L, Meglio M (1994) Increase of cerebral blood flow and improvement of brain motor control following spinal cord stimulation in ischemic spastic hemiparesis. Stereotact Funct Neurosurg 62: 103–107
28. Visocchi M, Cioni B, Meglio M (1996) Spinal cord stimulation impairs cerebral autoregulation. Acta Med Rom 28: 173–178
29. Visocchi M, Cioni B, Meglio M, Puca A, Vergari A, Marano G (1992) Modulation of cerebrovascular sympathetic tone during spinal cord stimulation: an experimental study. I International INS Congress Rome, Monduzzi ed Bologna, pp 59–63
30. Visocchi M, Bucci MG, Cioni B, Manni G, Meglio M, Puca A, Quaranta L (1992) Cerebral and ophthalmic haemodynamics during SCS I International INS Congress Rome. Monduzzi Bologna, pp 137–143
31. Visocchi M, Marano G, Cioni B, Meglio M (1994) Protective effects of SCS on early cerebral vasospasm in the rabbit. Preliminary results. IInd International INS Congress Goteborg, June 1–6
32. Visocchi M, Meglio M, Argiolas L, Pentimalli L, Cioni B (1996) Spinal cord stimulation prevents cerebral early vasospasm. An experimental study. III INS Congress Orlando March 6–10, 142
33. Visocchi M, Argiolas L, Meglio M, Cioni B, Dal Basso P, Rollo M, Cabezas Cuevas D (2001) Spinal cord stimulation and early experimental cerebral spasm: the functional monitoring and the preventing effect. Acta Neurochir (Wien) 143: 177–185
34. Visocchi M, Di Rocco C, Meglio M (2001) Protective effect of spinal cord stimulation on experimental early cerebral vasospasm. Conclusive results. Stereotact Funct Neurosurg 76: 269–275
35. Visocchi M, Giordano A, Calcagni M, Cioni B, Di Rocco C, Meglio M (2001) Spinal cord stimulation and cerebral blood flow in stroke: personal experience. Stereotact Funct Neurosurg 76: 262–268
36. Visocchi M, Tartaglione T, Romani R, Meglio M (2001) Spinal cord stimulation prevents the effects of combined ischemic and traumatic brain injury. An MR study. Stereotact Funct Neurosurg 76: 276–281

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Idiopathic syringomyelia: case report and review of the literature

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Summary

Syringomyelia is an uncommon disease that is caused most often by type I Chiari malformation, which develops in the hindbrain, and less frequently by other factors which are not limited to the hindbrain, including trauma, infection, or scoliosis. Idiopathic syringomyelia is rare. We present in this article a patient with idiopathic syringomyelia characterized by hypoesthesia and progressive weakness in the left lower limb. Decompression was attempted by means of laminectomy and a syringoarachnoid shunt. Motor, sensory, and bladder functions were monitored by the change in Japanese Orthopedic Association scores, which increased from 10 points preoperatively to 14 points 30 days postoperatively. This case demonstrates the effectiveness of surgical decompression in a patient with remarkable neurological deficit.

Keywords: Idiopathic syringomyelia; syringoarachnoid shunting; neurological deficit.

Introduction

The pathophysiology of syringomyelia (cavitation within the spinal cord) remains controversial [1–4]. Most cases have been associated with type I Chiari malformation. Others have been associated with typically noncongenital conditions, including scoliosis, arachnoiditis, and trauma. However, idiopathic syringomyelia is rare. Syringomyelia is more easily detected nowadays because of the availability of spinal magnetic resonance imaging (MRI). Before this technique became popular, the nonspecific and highly versatile signs and symptoms of syringomyelia – such as chronic pain, hyperhidrosis, hypertension, limb paresthesia, sensory loss, progressive weakness, and, in some cases, ascending paralysis [3, 5] – resulted in syringomyelia being easily overlooked, especially in patients with minor signs and symptoms. Consequently, most patients were diagnosed so late in the course of the disease that its neurological sequelae were irreversible.

Fortunately, the neurological deficits associated with syringomyelia can be reversed if decompression is carried out earlier in the course of the disease. In reviewing the literature on treatment options for this patient, we found that few articles had been reported about the nature and treatment of syringomyelia in Asia, especially in Taiwan. So, we would like to present a patient with idiopathic syringomyelia, his clinical course, treatment procedure and prognosis.

Case report

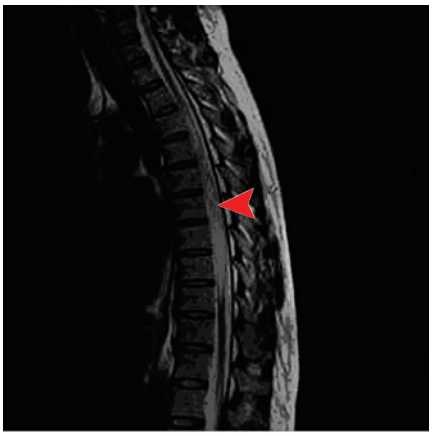
A 35-year-old male dentist had experienced gradually progressive weakness in his left leg since 5 years ago. The weakness exacerbated in the last 2 months and he had to use a cane when walking. A neurological examination revealed weakness in the left leg, especially dorsiflexion of the big toe, and hypoesthesia of pinprick and light touch sensation below the T7 dermatome on the left side of the body. The patient had no history of trauma, spinal tumor, or any evidence of spinal arachnoiditis. MRI studies revealed an inflated cord with a large cavity in the thoracic region of the spinal cord (T2–T9) (Fig. 1). Due to the recent exacerbation of his symptoms, we arranged surgical decompression for him.

Surgical technique

The first surgical procedure was T6–T8 laminectomy to expose the dura mater. The next procedure was to open the dura and a 1-mm midline myelotomy was performed with a microknife to create an opening for the cavitation. The fluid of the cavity was drained out and pressure was relieved, then we inserted an elastic catheter (18-gauge spinal stent: 2 cm in length, 1.24 mm in diameter) through this opening into the cavity in a cephalad direction and the caudal end placed in the dorsolateral subarachnoid space. We secured the tubing to the dura with 6-0 Prolene suture (Fig. 2).

Evaluation and follow-up of neurological function

The Japanese Orthopedic Association (JOA) scoring system was used to evaluate the neurological condition, specifically the peripheral motor activity (upper and lower extremities: 4 points, each), sensory activity



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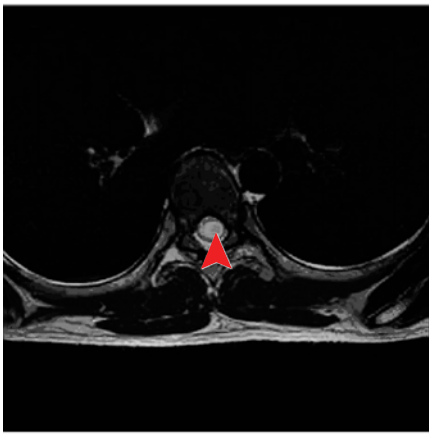

b

Fig. 1. Preoperative MRI, sagittal view (a) revealing a syrinx (arrow) with long thoracic extension (T2–T9). Axial view (b) revealing a large syrinx (arrow) with massive compression to cord (flattened appearance)

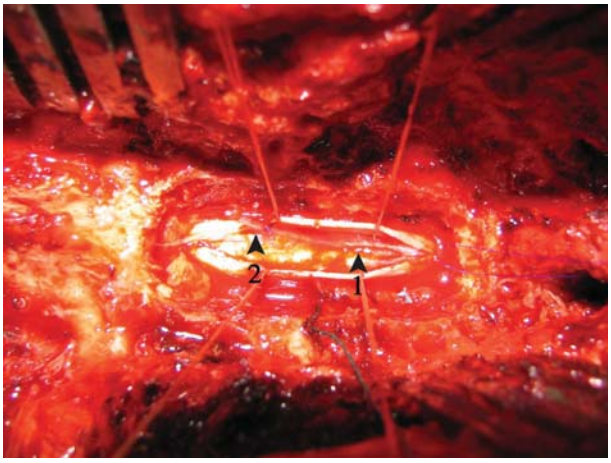

Fig. 2. Intraoperative findings. A bone window was made between T6 lamina and T8 lamina. A midline dural opening was made. Dorsal midline myelotomy was performed to open the syrinx. The shunt tube was placed into the syrinx (*arrow 1*) and the caudal end is of the catheter was secured to the dura with a 6-0 Prolene suture (*arrow 2*) (placed in the dorsolateral subarachnoid space)

Table 1. *Summary of the JOA scale grades for cervical myelopathy [23]**

Variable	Grade
I. Motor function	
a. Upper extremity	
unable to feed oneself	0
unable to handle chopsticks; able to eat with a spoon	1
handle chopsticks with much difficulty	2
handle chopsticks with slight difficulty	3
normal	4
b. Lower extremity	
unable to stand and walk by any means	0
unable to walk with a cane or other support on a level surface	1
walk independently on a level surface but need support on stairs	2
capable of fast walking but clumsy	3
normal	4
II. Sensory function	
a. Upper extremity	
apparent sensory loss	0
minimal sensory loss	1
normal	2
b. Lower extremity	
apparent sensory loss	0
minimal sensory loss	1
normal	2
c. Trunk	
apparent sensory loss	0
minimal sensory loss	1
normal	2
III. Bladder function	
a) Urinary retention and/or incontinence	0
b) Sense of retention and/or thin stream	1
c) Urinary retention and/or pollakiuria	2
d) Normal	3

* Cumulative normal grade in a healthy individual is 17.

(upper and lower extremities: 2 points each; trunk: 2 points), as urinary bladder function (3 points) before operation and on postoperative days (PODs) 7, 14, and 30 (Table 1). The recovery rate was calculated using the following formula:

Recovery rate (%) = (postoperative score − preoperative score) ÷ (17 − preoperative score) × 100.

Results

The JOA score was 10 points before surgery, 11 on POD 7, 12 on POD 14, and 14 on POD 30, and recovery

Table 2. *JOA score and recovery rate: pre-op and post-op*

Parameter	Pre-op	POD 7	POD 14	POD 30
JOA score	10	11	12	14
Muscle power (L foot dorsiflexion)	3	4−	4−	4
Recovery rate	–	14%	28%	57%

rates were 14, 28, and 57%, respectively. Strength in the left extensor hallucis longus muscle rose from grade 3 preoperatively to grade 4 by POD 30 (Table 2).

Discussion

Syringomyelia is characterized by dilation of the central canal in the spinal cord and results in neurological deficits because of gradual compression of the spinal cord. Its clinical presentation includes progressive weakness in the upper and/or lower extremities, diminished sensation, and chronic pain. People with this disorder are frequently misdiagnosed because of vague signs and symptoms. A delay in the diagnosis of this disorder can result in irreversible neurological deficits. These deficits can be reversed, however, by early and effective decompression of the spinal cord.

Current theories about the mechanism for the formation of syringomyelia are controversial. Possible mechanisms include perforation of the foramen of Magendie resulting in the subsequent expansion of the central canal (the Gardner theory) and the ''ball-valve'' effect of obstruction of the foramen magnum associated with type I Chiari malformations (the Williams theory) [6, 7]. Obstruction of the cerebrospinal pathway results in a pressure gradient [3, 5], which is relieved when pressure is dissipated through potential spaces. Eventually, this results in the creation of an intramedullary cavity [3, 5].

Conditions leading to syringomyelia can develop within the hindbrain or elsewhere [3, 8]. The most common hindbrain lesion that results in syringomyelia is type I Chiari malformation, which develops within the foramen magnum [9–13]. Spinal cord trauma, the second leading cause, can also lead to meningeal fibrosis and syringomyelia [3, 8, 14–16]. Other causes of syringomyelia do not necessarily involve the hindbrain such as spinal cord tumor, infection, kyphosis, and a reaction to iophendylate (Pantopaque) [3, 1, 4, 17]. In our patient, syringomyelia was classified as idiopathic after all these potential factors had been excluded.

The treatment strategy for patients with this disorder varies with the extent of disease progression. Some patients show no signs or symptoms during disease progression for many years; such patients may be treated conservatively [6, 7, 18–21]. Syringomyelia has been reported to resolve spontaneously with conservative treatment in a few cases [1, 6, 18, 21, 22], but some patients deteriorate progressively with that approach. Such patients may better be treated with surgical decompression, comprising myelotomy, syringosubarachnoid or syringopleural shunt, and spinal cord transaction [3]. In our patient, severe spinal cord compression induced several symptoms of syringomyelia, i.e. left foot drop and left-sided hypoesthesia, which worsened over 1 month. We performed a shunting procedure, which was followed by improvement in muscle strength in his left leg and improved sensation on the left side of his body. It has been reported that once neurological deficits develop in patients with syringomyelia, they cannot be completely reversed with surgery [1, 22]. However, our experience supports the concept that surgical decompression may be of some help for neurological deficits in patients with syringomyelia.

References

1. Kyoshima K, Bogdanov EI (2003) Spontaneous resolution of syringomyelia: report of two cases and review of the literature. J Neurosurg 53: 762–769
2. Iwasaki Y, Hida K, Koyanagi I, Abe H (2000) Reevaluation of syringosubarachnoid shunt for syringomyelia with Chiari malformation. J Neurosurg 46: 407–415
3. Goldstein JH, Kaptain GJ, Huy MD *et al* (1998) CT-guided percutaneous drainage of syringomyelia. J Comput Assist Tomogr 22: 984–988
4. Hilton EL, Henderson LJ (2003) Neurosurgical considerations in posttraumatic syringomyelia. AORN 77: 135–156
5. Sgouros S, Williams B (1996) Management and outcome of posttraumatic syringomyelia. J Neurosurg 85: 197–205
6. Andreas K, Thomas N, Helge T (2001) Spontaneous resolution of idiopathic syringomyelia. Neurology 57: 1519–1520
7. Sherman JL, Barkovich AJ, Citrin CM (1987) The MR appearance of syringomyelia: new observations. AJR Am J Roentgenol 148: 381–391
8. Sgouros S, Williams B (1995) A critical appraisal of drainage of syringomyelia. J Neurosurg 82: 1–10
9. Ball MJ, Dayan AD (1972) Pathogenesis of syringomyelia. Lancet 2: 799–801
10. Gardner WJ (1965) Hydrodynamic mechanism of syringomyelia: its relationship to myelocele. J Neurol Neurosurg Psychiatry 28: 247–259
11. Gardner WJ, Angel J (1959) The mechanism of syringomyelia and its surgical correction. Clin Neurosurg 6: 131–140
12. Williams B (1970) Current concepts of syringomyelia. Br J Hosp Med 4: 331–342
13. Williams B (1980) On the pathogenesis of syringomyelia: a review. J R Soc Med 73: 798–806
14. Caplan LR, Norohna AB, Amico LL (1990) Syringomyelia and arachnoiditis. J Neurol Neurosurg Psychiatry 53: 106–113
15. Stoodley MA, Gutschmidt B, Jones NR (1999) Cerebrospinal fluid flow in an animal model of non-communicating syringomyelia. J Neurosurg 44: 1065–1076
16. Schurch B, Wichmann W, Rossier AB (1996) Post-traumatic syringomyelia (cystic myelopathy): a prospective study of 449 patients with spinal cord injury. J Neurol Neurosurg Psychiatry 60: 61–67
17. Lee TT, Alameda GJ, Camilo E *et al* (2001) Surgical treatment of post-traumatic myelopathy associated with syringomyelia. Spine 26: 119–127

18. Sun JC, Steinbok P, Cochrane DD (2000) Spontaneous resolution and recurrence of a Chiari I malformation and associated syringomyelia: case report. J Neurosurg 92 [Suppl] 2: 207–210
19. Jack CRJ, Kokmen E, Onofrio BM (1991) Spontaneous decompression of syringomyelia: magnetic resonance imaging findings. Case report. J Neurosurg 74: 283–286
20. Santoro A, Delfini R, Innocenzi G *et al* (1993) Spontaneous drainage of syringomyelia: report of two cases. J Neurosurg 79: 132–134
21. Yeager BA, Lusser MA (1992) Spontaneous resolution of idiopathic syringomyelia: MR features. J Comput Assist Tomogr 16: 323–324
22. Bindal AK, Dunsker SB, Tew JM Jr (1995) Chiari I malformation: classification and management. J Neurosurg 37: 1069–1074
23. John KR, Paul RC (2003) Cervical laminoplasty: a critical review. J Neurosurg 98: 230–238

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Cell transplantation and nerve grafting

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Migration of bone marrow stem cells in ischaemic brain

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Summary

Stem cell therapy has been demonstrated to be effective in the management of haematological malignancy and solid cancer, but its role in neurodegenerative conditions remains uncertain. We hypothesize that: (1) ventricular delivery of bone marrow stem cells improves functional outcome in experimental ischaemia of the mouse brain; and (2) this improved outcome is due to migration of bone marrow stem cells to areas of ischaemia. Twelve mice with transient cerebral hemisphere ischaemia were randomly allocated to receive bone marrow stem cells or saline. The six animals that underwent cell therapy were found to perform better and committed fewer errors in the water maze system compared with the six control mice. Migration of these bone marrow stem cells was evident within the ventricular cerebro-spinal fluid (CSF) system and the brain parenchyma. This could also occur in clusters of cells. Preferential migration of these cells took place in lesioned areas.

Keywords: Bone marrow stem cells; cerebral ischaemia; water maze system.

Introduction

Stem cell therapy is generally regarded as a potential treatment modality for cancer and degenerative diseases. In neurodegenerative disorders such as stroke, spinal cord injury, Parkinson's disease and Alzheimer disease [5], consistent efficacy and its biological mechanism have not been worked out. In this study, two questions were asked: (1) Could the impaired learning and memory ability of the mice with transient cerebral ischaemia be improved by stem cell therapy? (2) If so, does migration of the stem cells into areas of cerebral ischaemia occur?

Material and methods

Twelve mice were selected for the experiment, where it took them approximately 90 seconds to pass the spatial learning and memory test using the water maze system after training [1, 6]. Cerebral hemisphere ischaemia was induced by a 20-minute occlusion of both common carotid arteries [2, 4]. Ten micro liter of 2.5×10^5 bone marrow-derived stem cells, labelled with bromodeoxyuridine (BrdU), were injected stereotactically into the right lateral ventricle of the mouse brain one day after ischaemia induction. Behavioural assessment of the ischaemic mice four weeks post-transplant was performed using the water maze system for five days. Animals were then euthanized. After reperfusion with paraformaldehyde, the brain was removed. Immunostaining of BrdU and NeuN were performed in frozen sections of 10 μm thickness.

Results

Compared with the control mice having sham operations, the time taken for completion of the behavioural assessment was significantly shorter (mean $\pm$ 1 standard deviation: 29 ± 10s vs 45 ± 13s; $p = 0.01$) and the incidence of errors committed on day five by ischaemic mice with undergone cellular therapy was significantly reduced (2 ± 1 vs 6 ± 2; $p = 0.001$). BrdU-labeled bone marrow stem cells were noted to migrate from the ventricular CSF system to the brain parenchyma (Fig. 1). Migration of $BrdU^+$ cells in clusters was also demonstrated in the lesioned brain where loss of neurons was demonstrated (Fig. 2).

Discussion/conclusion

Migration of implanted bone marrow stem cells occurs in an orderly and systematic fashion. The co-adhesion of the implanted cells led to cell clusters migrating to lesioned areas. These phenomena may be attributable to the micro-environment provided by the cerebral ischaemia. The development of successful cell therapy strategies for

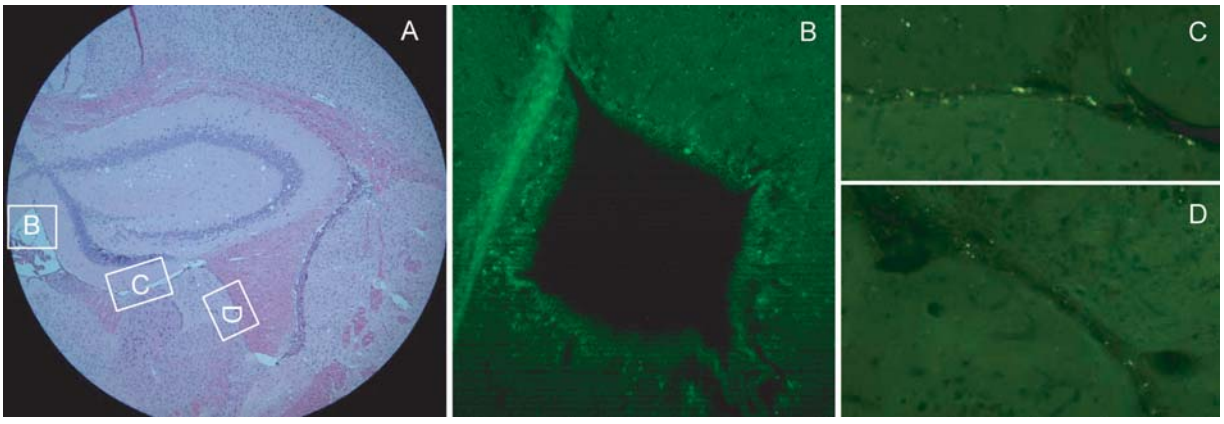

Fig. 1. Migration of implanted bone marrow stem cells to the parenchyma of the ventricular system. (A) H&E-stained brain section (B, C and D) migration of BrdU-labelled bone marrow stem cells to the highlighted area

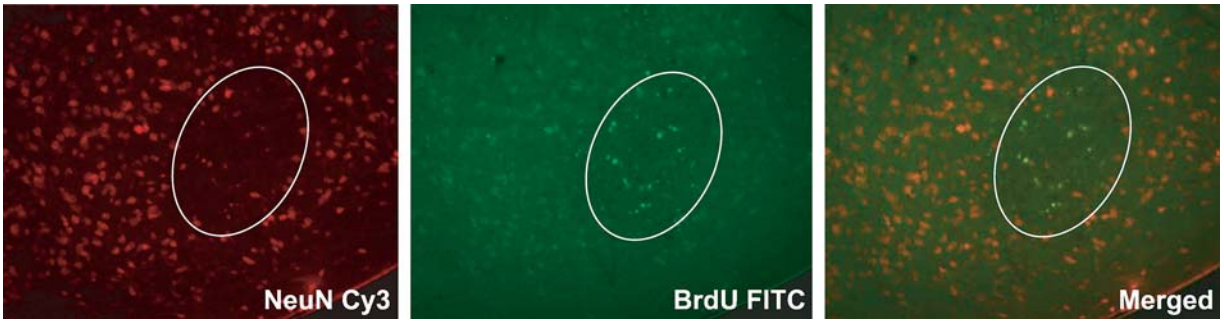

Fig. 2. Implantation of cell clusters to the lesioned area of the cortex

brain repair requires the elucidation of this ill-understood regulatory mechanism in the nervous system [3].

References

1. Gerlai R, McNamara A, Choi-Lundberg DL, Armanini M, Ross J, Powell-Braxton L, Phillips HS (2001) Impaired water maze learning performance without altered dopaminergic function in mice heterozygous for the GDNF mutation. Eur J Neurosci 14(7): 1153–1163
2. Gibson CL, Bath PM, Murphy SP (2005) G-CSF reduces infarct volume and improves functional outcome after transient focal cerebral ischemia in mice. J Cereb Blood Flow Metab 25(4): 431–439
3. Sun L, Lee J, Fine HA (2004) Neuronally expressed stem cell factor induces neural stem cell migration to areas of brain injury. J Clin Invest 113(9): 1364–1374
4. Terashima T, Namura S, Hoshimaru M, Uemura Y, Kikuchi H, Hashimoto N (1998) Consistent injury in the striatum of C57BL/6 mice after transient bilateral common carotid artery occlusion. Neurosurgery 43(4): 900–9007
5. Wei L, Cui L, Snider BJ, Rivkin M, Yu SS, Lee CS, Adams LD, Gottlieb DI, Johnson EM Jr, Yu SP, Choi DW (2005) Transplantation of embryonic stem cells overexpressing Bcl-2 promotes functional recovery after transient cerebral ischemia. Neurobiol 19(1–2): 183–193
6. Winter B, Bert B, Fink H, Dirnagl U, Endres M (2004) Dysexecutive syndrome after mild cerebral ischemia? Mice learn normally but have deficits in strategy switching. Stroke 35(1): 191–195

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The behavioral effect of human mesenchymal stem cell transplantation in cold brain injured rats

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Summary

We investigated the effect of stereotaxically transplanted human mesenchymal stem cells (hMSCs) on behavioral change after traumatic cold brain injury in adult rats. Cortical lesions ($n = 20$) were induced by touching a metal stamp, cooled with liquid nitrogen, to the dura over the forelimb motor cortex of adult rats. The procedure produced a localized lesion, and the animals showed significant motor deficits. hMSCs were freshly isolated from human iliac bone and cultured in tissue culture flasks with 10 ml Dulbecco's modified Eagle's medium. The animals received hMSC grafts (3×10^5 hMSCs) 6 days after cold lesion ($n = 10$). All rats were sacrificed 3 or 7 weeks after cold injury, and immunohistochemical staining was performed on brain sections to identify donor hMSCs.

Neurological evaluations were performed with the forepaw adjusting step test and modified neurological scoring. Treatment with 3×10^5 hMSCs improved the rat's neurological functions. We also found that the transplanted cells successfully migrated into the injured brain, preferentially localized around the injury site, and expressed the neuronal and astrocyte marker.

These data suggest that hMSCs may be a potential therapeutic tool for brain injuries.

Keywords: hMSCs; transplantation; behavior recovery; traumatic cold injury; immunostaining.

Introduction

Traumatic brain injury (TBI) is the most common brain injury in humans and involves mechanical, ischemic, and excitotoxic components [1, 2]. TBI results in motor and cognitive deficits that may persist for a prolonged period of time after the traumatic event. Following the initial mechanical damage, secondary pathways are activated that contribute to ischemic and excitotoxic damage [2–4]. Traumatic injury of the central nervous system, including events such as ischemia, edema, ionic imbalances, energy metabolism, and biochemical changes resulting in neurotoxicity that are harmful to brain cells, result in secondary neuronal dysfunction and death [5, 6]. These alterations are potentially harmful because they create a hostile environment and may also cause bystander effects to cells not exposed to the initial injury.

The primary goal of therapy after TBI is to ameliorate the destructive processes that begin with the injury. Traditional therapy for brain trauma involves the surgical removal of lesions and prevention of secondary complications. Regardless of the selected therapeutic intervention, trauma will always cause loss of neurons. Therefore, successful restoration of the injured brain must be accompanied with regeneration or transplantation of fetal embryonic stem cells. Brain tissue, marrow-derived stromal cells, neural stem cells, or other genetically engineered cells are capable of integration and differentiation to restore functional connectivity [7–11]. One of these cell types, adult stem cells, has been located in several human organs such as bone marrow, blood, cornea, retina, brain, skeletal muscles, liver, and skin. Stem cells located in continuously renewing tissues are able to regenerate or repair tissues throughout life. However, neural stem cells (NSC) of the non-regenerating adult central nervous system (CNS) exhibit poor capacity to generate new neurons to replace cells lost after injury or degeneration. Some stem cells may have the capacity to differentiate, but the mechanism of restoration is not clear. One possibility is that the progenitor cells integrate into the brain and take over the function of the neurons or glia that were destroyed by injury. Another is that the transplanted cells provide support to injured cells, and protection to host cells.

In recent years, there has been increasing interest in MSCs, because they may have several potential therapeutic applications. In addition to their ability to support

hematopoiesis, MSCs can differentiate into tenocytes, adipocytes, osteocytes, chondrocytes, and smooth muscle cells [12, 13]. They also have the ability to secrete growth factors [14, 15], and their potential for central nervous system repair has been recognized [16, 17].

Bone marrow is a relatively accessible source of autologous hematopoietic stem cells with which there are extensive clinical trials. In a recent discovery, adult human bone marrow-derived cells can be easily expanded in vitro and manipulated via their culture conditions to express markers associated with cells of neuroectodermal lineage [18–20].

However, the functionality of neural markers does not directly imply that bone marrow-derived cells injected into focal areas of cerebral ischemia [21] or infused peripherally [22] will lead to functional improvements. Similarly, rodent studies have demonstrated that focal implantation or intravenous infusion of bone marrow cells can lead to remyelination in the spinal cord [23].

In the previous study, rodent bone marrow cells migrated into the brain and differentiated into microglia and astrocytes when transplanted into previously irradiated recipients [13, 14]. Also, when implanted into the lateral ventricle or striatum of mice, cultured marrow stromal cells migrate into the brain and differentiate into astrocytes [15, 16].

In the present study, we examined the cell growth kinetics and expansion of hMSCs in vitro as well as investigated the effect of hMSCs transplanted stereotaxically on functional outcomes in animals after traumatic brain injury. This represents an extension of our research evaluating the potential use of MSCs as a therapy for TBI.

Materials and methods

Isolation and culture of hMSCs

Bone marrow aspirates were obtained by puncturing the posterior iliac crest of human donors under local anesthesia, and hMSC growth and expansion were then examined in vitro. Each 10 ml of aspirate was diluted with 10 ml of Hanks' balanced salt (HBS; Gibco, Invitrogen, NY, USA) solution and washed by gentle inversion several times. Mononuclear cells of bone marrow specimens were separated on a ficoll density gradient (Ficoll-Paque, Pharmacia, CA, USA). About 5 ml of ficoll was layered beneath 20 ml of sample and spun at 800 g for 30 min at room temperature. The mononuclear cell layer was removed from the gradient interface and washed twice with Hank's balanced salt solution. Cells were spun at 3000 rpm for 5 min and resuspended in glucose Dulbecco's modified Eagle's medium (DMEM; Gibco-BRL, Grand Island, NY) with 10% FBS (Hyclone, Logan, Utah, USA) and 1% penicillin streptomycin (Gibco, Invitrogen, NY, USA). Cells were plated in a 25 cm^2 tissue culture flask and incubated at 37 °C with 5% humidified CO_2. After 24 h, non-adherent cells were removed. Adherent cells were washed twice with PBS and shaken to remove adherent hematopoietic precursors, and fresh DMEM medium was added. The medium was changed every other day and the cells were grown to 70–90% confluence. Cells were harvested with 0.05% trypsin-EDTA for 5 min at 37 °C. Cells were then replated in a 75 cm^2 flask, and again grown in DMEM medium supplemented with bFGF (10 ng/ml, Sigma, St. Louis, MO, USA).

The plastic-adherent hMSCs were split on day 10 (90% confluence) and every 8–9 days after that to assess cell growth and yield.

Immunocytochemistry

Cultured cells were fixed with 4% paraformaldehyde in PBS and were incubated with primary antibodies overnight at 4 °C. The following primary antibodies were used: monoclonal anti-glial fibrillary acidic protein (GFAP 1:200; Sigma, St. Louis, MO, USA), monoclonal mouse anti-neurofilament protein (NF 1:40; Dako, Denmark), neuron-specific class III β-tubulin (Tuj1) monoclonal (1:400; Covance, CA, USA), and Map-2 monoclonal (1:200; Sigma, St. Louis, MO, USA). For detection of primary antibodies, fluorescently labeled Cy3-conjugated IgG secondary antibodies (Jackson Immuno Research, West Grove, PA, USA) were incubated for 2 h at room temperature. Cells were mounted in VECTASHIELD containing 4,6-diamidino-2-phenylindole (DAPI; Vector Laboratories, Burlingame, CA, USA) and images were obtained via confocal microscope.

Experimental group

Rats were divided into 3 experimental groups: (i) normal group, 5 rats without cold lesions; (ii) control group, only cold lesioned rats ($n = 15$); (iii) a cold lesioned group transplanted with hMSCs in the motor cortex ($n = 15$). To examine the change of behavioral recovery, all 3 groups were behaviorally tested at 2, 4, and 6 weeks after hMSC transplantation. Rats were then sacrificed 6 weeks after transplantation for immunohistochemistry analysis to confirm hMSC integration into host tissue.

Surgical procedures and behavioral testing

Five animals per group were housed in a temperature-controlled clean room on a 12-h light/dark schedule with free access to food and water. Male adult Sprague-Dawley rats weighing 250–280 g were used for the cold brain injured rat model. Under a mixture of ketamine (75 mg/kg), acepromazine (0.75 mg/kg), and rompun (4 mg/kg) anesthesia, the head was fixed in a stereotaxic frame. The scalp was incised and a circular craniectomy was made over the right forelimb motor cortex (± 2 mm anterior and posterior from bregma, 3 mm lateral from the midline). Special care was taken to keep the dura intact to prevent bleeding. The cold lesion stamp was pre-cooled to -70 °C with liquid nitrogen, and then touched to the exposed dura for 30 sec, 3 times. The skin was closed over the lesion. We confirmed the injured lesion with TTC (2,3,5-triphenyltetrazolium chloride; Sigma, St. Louis, MO, USA) staining because living cells reduce tetrazole to a water-insoluble red colored formazan, resulting in dead and living tissue being differentiated based on their respective colors [24].

One day after cold lesion injury, animals were behaviorally tested to confirm the injured motor cortex. Neurological scoring was examined using the rat stroke motor score [25] with modifications to measure forelimb function specifically. We also assessed contralateral forepaw adjusting steps on a treadmill, which moved at a rate of 90 cm/12 sec, as described in a previous study [26]. This test consisted of 5 trials alternating between each forepaw at the 2nd, 4th, and 6th week after hMSC transplantation in the injured rat models.

Preparation of cells for transplantation

Cells were used for transplantation at the 3rd passage and were labeled with a pulse of 10 M 5-bromodeoxyuridine (BrdU; Sigma,

St. Louis, MO, USA), which was added to the culture medium 48 h before transplantation. Cells were trypsinized at 37 °C for 5 minutes with 0.05% trypsin-EDTA, and the dissociated cells were resuspended in PBS. Using a sterilized stainless steel needle (0.3 mm O.D.) connected to a Hamilton microsyringe, 3 µl of the cell suspension (5×10^4 cells/µl) was injected into the cortex at 2 sites (AP; ±1 mm, ML; +1.1 mm, DV; 2.0 mm) over a period of 4 min. A time lapse of 4 min before the removal of the needle allowed the cells to settle within the injection site. The rats were given a daily injection of cyclosporin A (10 mg/kg, i.p. Chong Kun Dang. Pharm., Seoul, Korea) 24 h before grafting, which was continued until sacrifice.

Immunohistochemical assessment of transplanted hMSCs

Following the 6th week behavioral test, rats were anesthetized with 25% urethane (Sigma, St. Louis, MO, USA) in PBS and intracardially perfused with 125 ml of normal saline followed by 250 ml of ice-cold 4% paraformaldehyde in phosphate-buffered saline (pH 7.4, PBS). The brains of all anesthetized rats were removed and post-fixed in the same fixative for an additional day at room temperature. Tissues were transferred to 30% sucrose in PBS and immersed for 48 h at 4 °C. They were then frozen in O.C.T. compound (Tissue-Tek, Sakura Finetk, Torrance, CA, USA) at −20 °C and sectioned (section thickness 35 µm) using a freezing microtome. To detect BrdU, sections were incubated in 2N HCl for 1 h at 37 °C before the staining procedure. For double staining with BrdU, other cell type specific markers were used and visualized by a green color. The primary antibodies used were: BrdU-FITC monoclonal (1:200, Serotec, Oxford, UK), neuronal nuclei (NeuN) monoclonal (1:100; Chemicon, Temecula, CA, USA), neuron-specific class III β-tubulin (Tuj1) monoclonal (1:400; Covance, CA, USA), Map-2 monoclonal (1:200; Sigma, St. Louis, MO, USA), monoclonal anti-glial fibrillary acidic protein (GFAP 1:200; Sigma, St. Louis, MO, USA), and monoclonal mouse anti-neurofilament protein (NF 1:40; Dako, Denmark). For primary antibody detection, a 2-h room temperature incubation with fluorescently-labeled CY3-conjugated IgG secondary antibody (Jackson Immuno-research Lab.) was performed, and images were then obtained via confocal microscope.

Data analysis

Statistical analysis was performed with SPSS version 9.0 statistical software (SPSS Inc., Chicago, IL, USA). Firing rate comparisons from different rats in each group were performed using analysis of variance (ANOVA). Results showing significant differences between groups were compared using Kruskal-Wallis one-way ANOVA and then a Mann-Whitney U-test. Statistical significance was accepted when p was <0.05.

Results

Isolation and culture of hMSCs and Immunochemistry

To examine hMSC growth kinetics and expansion in vitro, we obtained bone marrow aspirates from the posterior iliac crest of human donors under local anesthesia. As described in the methods section, hMSCs were expanded in DMEM medium in the presence of bFGF for 8–10 days, incubated at 37 °C with 5% humidified CO_2, and then fixed. Figure 1 shows immunocytochemical stainings of cultured hMSCs with the following primary antibodies: GFAP (Fig. 1A; glial fibrillary acidic protein in astrocyte), Tuj1 (Fig. 1B; neuron specific beta III isoform of tubulin), MAP-2 (Fig. 1C; microtubule associated protein-2 confined to neuronal cell bodies and dendrites), and NF (Fig. 1D; neurofilament) with red color. Cell nuclei were counterstained with DAPI

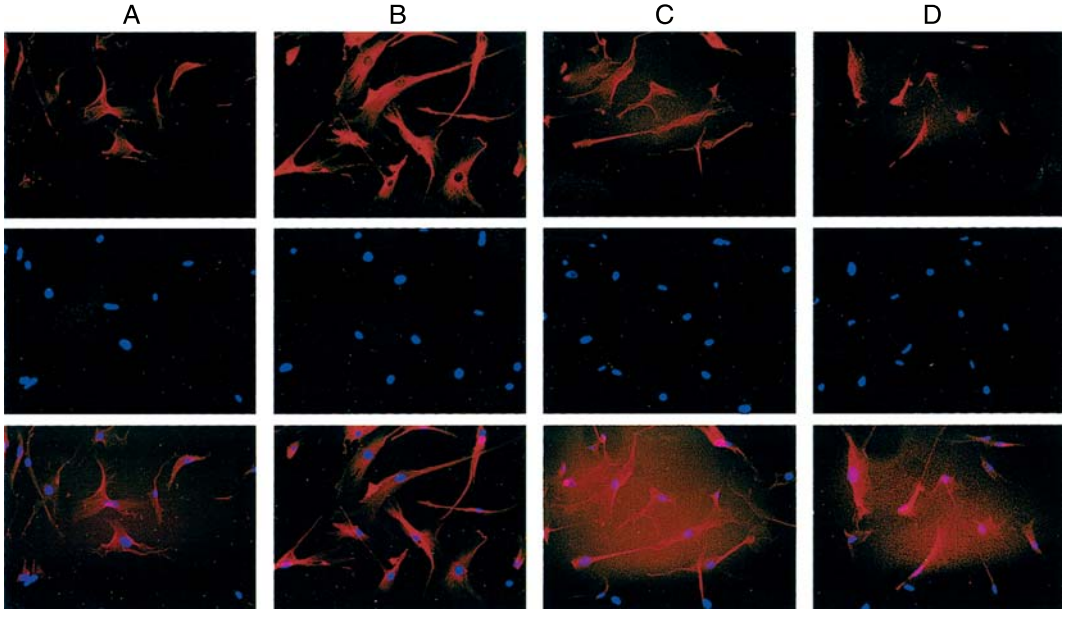

Fig. 1. Double immunocytochemical expressed confocal image of hMSCs. hMSCs were grown in the presence of bFGF. (A) Immunocytochemistry with GFAP, (B) Tuj1, (C) MAP-2 and (D) NF (red images). Blue images are cell nuclei counterstained with DAPI

(blue). Confocal microscope images contain long projections of immunoreactive filamentous structures that are visible in the cytoplasm. The number of MAP-2 and NF positive cells was less than GFAP and Tuj1 positive populations.

Characterization of the brain cortex after cold lesion and after hMSC graft

The pre-cooled stamp caused a wedge-like lesion that penetrated all layers of the cortex. The lesion affected the right forelimb motor cortex and resulted in a motor deficit in the left forelimb. The place and depth of cold lesioned brain were determined by observation of TTC-stained sections. As shown in Fig. 2, the control lesioned group was perfused 6 days after injury and we found that the lesion formed a central necrotic area with edema. Lesions were surrounded by a zone of reactive astrocytes that displayed a heavily up-regulated expression of GFAP (Fig. 2B). In contrast, animals transplanted with hMSCs demonstrated a smaller injured cavity than the control groups (Fig. 2C).

Functional recovery by transplanted hMSCs

One day after cold lesion injury, animals were tested to confirm the motor cortex injured rat model. Cold injured rat models were selected for transplantation by quantification of forepaw adjusting steps and sum neurological score. The animals demonstrated a similar degree of impairment in both behavioral tests one day after motor cortex injury. Behavior tests were also performed at the 2nd, 4th, and 6th week after hMSC transplantation. A neurological score is the sum of scores including symmetry movement, forelimb flexion angle, and climb score, as described by Garcia *et al.* [25].

In the injured rat models grafted with hMSCs, the number of forepaw adjusting steps was significantly increased 2 weeks after injury (control group: 4.03 ± 2.1, grafted group: 10.67 ± 3.8, $^{*}p < 0.05$) (Fig. 3A).

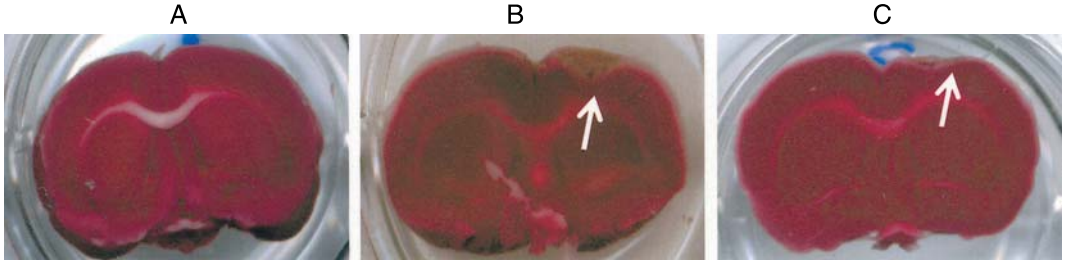

Fig. 2. Characterization of the brain cold lesion before grafting. (A) Normal group, (B) cold lesioned group, (C) hMSCs transplanted group

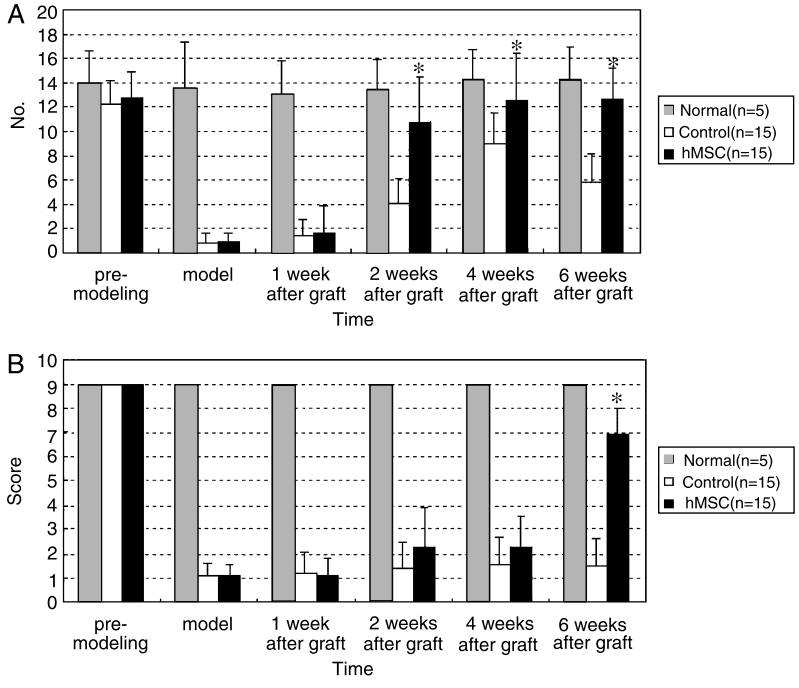

Fig. 3. Time course of behavioral recovery after hMSC transplantation (A) forepaw adjusting step test. Behavior test scores were evaluated at 2, 4, and 6 weeks post-transplantation and compared to pre-transplantation values. (B) Sum of neurological score including symmetry movement, forelimb flexion angle, and climb tests. Values are means $\pm$ SEM ($^{*}p < 0.05$)

Table 1. *Exchange of neurological score in experimental groups*

	Pre-modeling	Model	1 week after graft	2 week after graft	4 week after graft	6 week after graft
Symmetry movement score						
Normal ($n=5$)	3	3	3	3	3	3
Control ($n=15$)	3	1	1.1 ± 0.32	1.2 ± 0.42	1.3 ± 0.48	1.4 ± 0.52
hMSCs ($n=15$)	3	1	1	$2.17 \pm 0.83^*$	$2.42 \pm 0.51^*$	$2.58 \pm 0.51^*$
Forelimb flexion angle score						
Normal ($n=5$)	3	3	3	3	3	3
Control ($n=15$)	3	1	1	1.3 ± 0.48	1.5 ± 0.53	1.4 ± 0.52
hMSCs ($n=15$)	3	1	1.08 ± 0.28	$2.5 \pm 0.67^*$	$2.5 \pm 0.67^*$	$2.42 \pm 0.67^*$
Climb score						
Normal ($n=5$)	3	3	3	3	3	3
Control ($n=15$)	3	1.3 ± 0.48	1.5 ± 0.52	1.7 ± 0.48	1.8 ± 0.63	1.7 ± 0.67
hMSCs ($n=15$)	3	1.25 ± 0.45	1.3 ± 0.49	2.16 ± 0.71	1.9 ± 0.51	1.8 ± 0.57

We examined using the rat stroke motor score with modifications to measure forelimb function specifically at the 2nd, 4th, and 6th week after hMSC transplantation in the injured rat models. The symmetry movement and forelimb flexion angle scores were significantly increased from 2 weeks after injury, but the climb score did not improve.

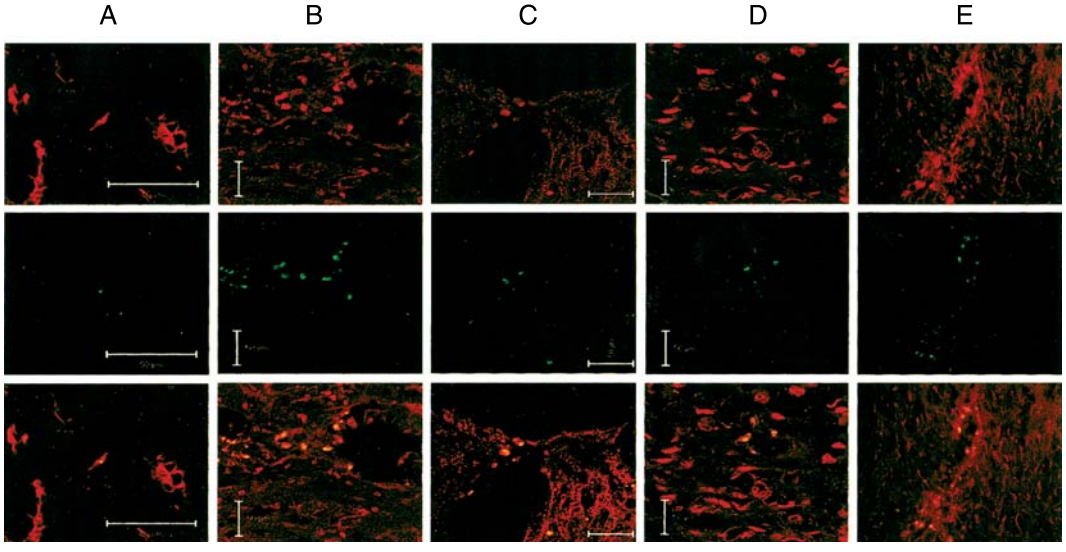

Fig. 4. Confocal microscopic images for several antibody stained motor cortex sections (section thickness is 35 μm) of injured rat models grafted with hMSCs. Immunohistochemical staining and antibodies are as follows (red image); (A) GFAP positive cells around injured area, (B) APC, (C) MAP-2, (D) NeuN, and (E) NF. Green images are BrdU positive cells. Scale bar is 50 μm

Also, the animal models grafted with hMSCs, demonstrated significantly higher neurological scores 6 weeks after injury (control group: 1.5 ± 1.13, grafted group: 6.92 ± 1.08, $^*p < 0.05$) (Fig. 3B). The symmetry movement and forelimb flexion angle scores were significantly increased 2 weeks after injury, but the climb score did not improve (Table 1).

Immunohistochemical characterization of the transplant and surrounding implantation

BrdU pre-labeled hMSCs were observed in the implantation site and surrounding areas of injury 6 weeks after transplantation. BrdU positive cells were immunoreactive for several neural specific markers (A; GFAP, B; APC, C; MAP2, D; NeuN, and E; NF), as shown in Fig. 4. These results show that the transplanted BrdU-pre-labeled hMSCs, although small in population, have successfully grafted the lesion, integrated well within the host brain, and differentiated into neural lineage cells (neurons and astrocytes) in vivo.

Discussion

Brain trauma leads to the production of free radicals, excitotoxicity, calcium overloading, cytokine secretion,

growth-factor activation or withdrawal, and other possible reactions that are harmful to brain cells [27, 28]. These alterations are potentially harmful because they create a hostile environment and may also cause bystander effects to cells not exposed to the initial trauma. The emerging field of regenerative medicine represents an alternative approach to the more traditional pharmacological therapy for restoration of damaged tissues. Recently, MSCs have been studied in vitro and used as a cell source to repair CNS disease and other organ disorders in vivo [16, 18, 29, 30]. These cells have been studied because of their ability to differentiate into non-mesodermal lineage cells and their possible use as vehicles for autotransplantation and gene therapy for various diseases. The present study has demonstrated that hMSCs, which have the potential to give rise to a variety of neuronal cells, can affect functional recovery in the motor cortex injured rat model. hMSCs transiently or continuously expressed several neural specific markers (GFAP, MAP-2, NeuN, APC, and NF), but have a limited population. Also, hMSCs significantly reduced the magnitude of behavioral impairment observed by the forepaw adjusting step and neurological tests, compared to media transplanted animals. This result supports the claim that hMSCs have a multi-potential ability.

Until recently, adult cells have been thought to be restricted to their tissues of origin. Cells are well known to be capable of repairing damage in tissues in which they reside, such as blood, muscle, liver, and skin. However, the finding that adult cells could be reprogrammed to express genes typical of all three differentiated lineage cell types (mesoderm, endoderm, and ectoderm) when fused to cells in heterokaryons was quite unexpected [31].

Our data demonstrate that following hMSC grafting, increased neurogenesis was observed within the implanted areas of the brain. The functional outcome of hMSC-treated animals was also significantly improved. There was also improvement in functional outcome, which was not only maintained but became more significant with time. We used BrdU as a marker of grafted cells. BrdU is a thymidine analog that is incorporated within the deoxyribonucleic acid of replicating cells. It is possible that hMSCs, which graft and migrate into the brain, may proliferate, pick up BrdU, and stain positively.

The brain sections from hMSC recipient rats were double-stained with neuronal-specific antibodies and BrdU. Cells that were positive for both neuronal markers and BrdU were observed, although in very small populations, whereas functional recovery was significantly improved. Some of the grafted cells expressed phenotypic features of neurons and astrocytes, but their number was small, and the probability of their integration into functional neural circuitry is low. The functional benefit obtained as a result of hMSC transplantation may be due to the production of neurotrophic growth factors [12]. The functional improvement in animals that received hMSC transplants was not dependent on establishing new neuronal circuits between grafts and the host, or dependent on reducing the injury site size. This fact suggests that functional restoration was probably a result of proteins released by grafted hMSCs that promoted brain plasticity in the host brain.

Neurotrophic growth factors are essential for the proliferation and maturation of neurons, and hMSCs can produce these growth factors both in vitro and in vivo [2, 12]. As Mahmood *et al.* reported, hMSCs normally secrete brain-derived neurotrophic factor, nerve growth factor, basic fibroblast growth factor, vascular endothelial growth factor, and hepatocyte growth factor when cultured in isolation. However, this secretion was significantly enhanced when TBI extracts of rat brain were added to the culture media [32].

Li *et al.* treated an ischemic stroke rat model with intravenous hMSC injection and found in vivo production of nerve growth factor and brain-derived neurotrophic factor by hMSCs, which correlated with improvement in functional outcome [17]. Recent data indicate that growth factors such as brain-derived neurotrophic factor, basic fibroblast growth factor, and vascular endothelial growth factor promote neurogenesis [33–36]. Growth factors are expressed intracellularly and are also secreted by cells into the extracellular matrix. They interact with specific cell surface receptors, and the ensuing signal transduction activates second messenger systems, with subsequent initiation of new gene expression leading to new cell function.

We are aware of the problem of immune rejection of human cells in rats, but no significant immune response against hMSCs was observed in vivo. In a related study of hMSCs, it was found that rats were not sensitized against hMSCs after intravenous transplantation of hMSCs in rats subjected to cerebral ischemia [12]. There is also the possibility that hMSCs secrete mediators that decrease the immune responses involved in xenograft rejection [1].

Our study clearly shows that the transplantation of hMSCs can be a potential treatment for functional recovery after TBI. hMSCs can be obtained from human

bone marrow, expanded in culture, and used as a therapeutic source. Success in TBI treatment with hMSC transplantation may eventually be expanded to treat a wide variety of neurological disorders. Further study is needed to investigate how MSCs affect other neural restorative functions such as synaptogenesis and angiogenesis.

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References

1. McIntosh TK, Smith DH, Meaney DF, Kotapka MJ, Gennarelli TA, Graham Di (1996) Neuropathological sequelae of traumatic brain injury: relationship to neurochemical and biomechanical mechanisms. Lab Invest 74: 315–342
2. Kawamata T, Katayama Y, Hovda DA, Yoshino A, Becker DP (1995) Lactate accumulation following concussive brain injury: the role of ionic fluxes induced by excitatory amino acids. Brain Res 674: 196–204
3. Azbill RD, Mu X, Bruce-Keller AJ, Mattson MP, Springer JE (1997) Impaired mitochondrial function, oxidative stress and altered antioxidant enzyme activities following traumatic spinal cord injury. Brain Res 765: 283–290
4. Xiong Y, Gu Q, Peterson PL, Muizelaar JP, Lee CP (1997) Mitochondrial dysfunction and calcium perturbation induced by traumatic brain injury. J Neurotrauma 14: 23–34
5. Anderson DK, Hall ED (1993) Pathophysiology of spinal cord trauma. Ann Emerg Med 22: 987–992
6. Tator CH, Fehlings MG (1991) Review of the secondary injury theory of acute spinal cord trauma with emphasis on vascular mechanisms. J Neurosurg 75: 15–26
7. Kesslak JP, Brown L, Steichen C, Cotman CW (1986) Adult and embryonic frontal cortex transplants after frontal cortex ablation enhance recovery on a reinforced alternation task. Exp Neurol 94: 615–626
8. Kesslak JP, Nieto-Sampedro M, Globus J, Cotman CW (1986) Transplants of purified astrocytes promote behavioral recovery after frontal cortex ablation. Exp Neurol 92: 377–390
9. Muir JK, Raghupathi R, Saatman KE, Wilson CA, Lee VM, Trojanowski JQ, Philips MF, McIntosh TK (1999) Terminally differentiated human neurons survive and integrate following transplantation into the traumatically injured rat brain. J Neurotrauma 16: 403–414
10. Netto CA, Hodges H, Sinden JD, LePeillet E, Kershaw T, Sowinski P, Meldrum BS, Gray JA (1993) Foetal grafts from hippocampal regio superior alleviate ischaemic-induced behavioural deficits. Behav Brain Res 58: 107–112
11. Stein DG, Palatucci C, Kahn D, Labbe R (1988) Temporal factors influence recovery of function after embryonic brain tissue transplants in adult rats with frontal cortex lesions. Behav Neurosci 102: 260–267, 325–326
12. Bjorklund A, Lindvall O (2000) Cell replacement therapies for central nervous system disorders. Nat Neurosci 3: 344–544
13. Theele DP, Streit WJ (1993) A chronicle of microglial ontogeny. Glia 7: 5–8
14. Eglitis MA, Mezey E (1997) Hematopoietic cells differentiate into both microglia and macroglia in the brains of adult mice. Proc Natl Acad Sci USA 94: 4080–4085
15. Azizi SA, Stokes D, Augelli BJ, DiGirolamo C, Prockop DJ (1988) Engraftment and migration of human bone marrow stromal cells implanted in the brains of albino rats-similarities to astrocyte grafts. Proc Natl Acad Sci USA 95: 3908–3913
16. Kopen GC, Prockop DJ, Phinney DG (1999) Marrow stromal cells migrate throughout forebrain and cerebellum, and they differentiate into astrocytes after injection into neonatal mouse brains. Proc Natl Acad Sci USA 96: 10711–10716
17. Li Y, Chen J, Chen XG, Wang L, Gautam SC, Xu YX, Katakowski M, Zhang LJ, Lu M, Janakiraman N, Chopp M (2002) Human marrow stromal cell therapy for stroke in rat: neurotrophins and functional recovery. Neurology 59: 514–523
18. Mezey E, Chandross KJ, Harta G, Maki RA, McKercher SR (2000) Turning blood into brain: cells bearing neuronal antigens generated in vivo from bone marrow. Science 290: 1779–1782
19. Woodbury D, Schwarz EJ, Prockop DJ, Black IB (2000) Adult rat and human bone marrow stromal cells differentiate into neurons. J Neurosci Res 61: 364–370
20. Bonilla S, Alarcon P, Villaverde R, Aparicio P, Silva A, Martinez S (2002) Haematopoietic progenitor cells from adult bone marrow differentiate into cells that express oligodendroglial antigens in the neonatal mouse brain. Eur J Neurosci 15: 575–582
21. Zhao LR, Duan WM, Reyes M, Keene CD, Verfaillie CM, Low WC (2002) Human bone marrow stem cells exhibit neural phenotypes and ameliorate neurological deficits after grafting into the ischemic brain of rats. Exp Neurol 174: 11–20
22. Chen J, Li Y, Wang L, Zhang Z, Lu D, Lu M, Chopp M (2001) Therapeutic benefit of intravenous administration of bone marrow stromal cells after cerebral ischemia in rats. Stroke 32: 1005–1011
23. Akiyama Y, Radtke C, Honmou O, Kocsis JD (2002) Remyelination of the spinal cord following intravenous delivery of bone marrow cells. Glia 39: 229–236
24. Hortobagyi T, Hortobagyi S, Gorlach C, Harkany T, Benyo Z, Gorogh T, Nagel W, Wahl M (2000) A novel brain trauma model in the mouse: effects of dexamethasone treatment. Pflugers Arch 441: 409–415
25. Garcia JH, Wagner S, Liu KF, Hu XJ (1995) Neurological deficit and extent of neuronal necrosis attributable to middle cerebral artery occlusion in rats. Statistical validation. Stroke 26: 627–634
26. Chang JW, Wachtel SR, Young D, Kang UJ (1999) Biochemical and anatomical characterization of forepaw adjusting steps in rat models of Parkinson's disease: studies on medial forebrain bundle and striatal lesions. Neuroscience 88: 617–628
27. Holmin S, Mathiesen T (2000) Intracerebral administration of interleukin-1 beta and induction of inflammation, apoptosis, and vasogenic edema. J Neurosurg 92: 108–120
28. McIntosh TK, Saatman KE, Raghupathi R, Graham DI, Smith DH, Lee VM, Trojanowski JQ (1998) The Dorothy Russell Memorial Lecture. The molecular and cellular sequelae of experimental traumatic brain injury: pathogenetic mechanisms. Neuropathol Appl Neurobiol 24: 251–267
29. Tomita S, Li RK, Weisel RD, Mickle DA, Kim EJ, Sakai T, Jia ZQ (1999) Autologous transplantation of bone marrow cells improves damaged heart function. Circulation 100: II247–II256
30. Park KW, Eglitis MA, Mouradian MM (2001) Protection of nigral neurons by GDNF-engineered marrow cell transplantation. Neurosci Res 40: 315–323
31. Spear BT, Tilghman SM (1990) Role of alpha-fetoprotein regulatory elements in transcriptional activation in transient heterokaryons. Mol Cell Biol 10: 5047–5054

32. Mahmood A, Lu D, Lu M, Chopp M (2003) Treatment of traumatic brain injury in adult rats with intravenous administration of human bone marrow stromal cells. Neurosurgery 53: 697–702
33. Jin K, Zhu Y, Sun Y, Mao XO, Xie L, Greenberg DA (2002) Vascular endothelial growth factor (VEGF) stimulates neurogenesis in vitro and in vivo. Proc Natl Acad Sci USA 99: 11946–11950
34. Lee J, Duan W, Mattson MP (2002) Evidence that brain-derived neurotrophic factor is required for basal neurogenesis and mediates, in part, the enhancement of neurogenesis by dietary restriction in the hippocampus of adult mice. J Neurochem 82: 1367–1375
35. Menard C, Hein P, Paquin A, Savelson A, Yang XM, Lederfein D, Barnabe-Heider F, Mir AA, Sterneck E, Peterson AC, Johnson PF, Vinson C, Miller FD (2002) An essential role for a MEK-C/EBP pathway during growth factor-regulated cortical neurogenesis. Neuron 36: 597–610
36. Tao Y, Black IB, DiCicco-Bloom E (1993) Neurogenesis in neonatal rat brain is regulated by peripheral injection of basic fibroblast growth factor (bFGF). J Comp Neurol 376: 653–663

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Effect of human mesenchymal stem cell transplantation combined with growth factor infusion in the repair of injured spinal cord

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Summary

Recently, bone marrow stromal cells have been shown to have the capacity to differentiate into neural cell under experimental cell culture conditions. Some investigators suppose that these cells, when placed into an environment of injury, express factors that promote repair or active compensatory mechanisms and endogeneous stem cells within the injured tissue [2, 3]. Rats were subjected to a weight driven implant spinal cord injury. After one week, the rats were treated with cultured human mesenchymal stem cells (MSCs) transplantation and basic fibroblast growth factor (bFGF) infusion into the CSF space. Functional outcome and histologic evaluation were performed. The data showed improved functional outcome in the group treated with MSCs transplantation and bFGF administration compared with the group of MSCs transplantation and control, which means bFGF might take an additional role to improve functional outcome. Glial differentiation of MSCs was noted but neuronal differentiation was doubtful. In this study, we did not demonstrate the mechanism of the neurotrophic factor affecting neural repair. However, this study is consistent with growing literature that MSCs and neurotrophic factor promote tissue repair and functional recovery after spinal cord injury and suggests that MSCs transplantation and bFGF warrants investigation as a therapeutic intervention after spinal cord injury.

Keywords: Spinal cord injury; human mesenchymal stem cell; growth factor; transplantation; behavioral test.

Introduction

Bone marrow stromal cell (MSC) is an adult stem cell which may be a candidate for cell therapy to treat CNS injury. It is reported that transplantation of marrow stromal cells (MSCs) can promote functional recovery of the injured spinal cord [2–4, 6, 7]. However, the mechanisms of these actions are not clearly defined. Possible mechanisms are as follows: 1) secretory factors by MSCs prevent apoptosis of damaged neuron and promote neuronal survival (neuroprotective effect) 2) secretion of growth factor for axonal regeneration or increasing sprouting for plasticity 3) secretion of trophic factor for replacement of damaged cell or tissue from endogenous neural stem cell 4) MSCs originated from bone marrow differentiate and replace the damaged cell or tissue 5) forming of the supportive structure that guides axonal regeneration 6) increasing myelination of damaged axon through differentiated myelinating cell or increasing schwann cell activity. Many growth factors are involved in the neuroprotective and neuroregenerative effect in the injured spinal cord. This study investigates whether a combined treatment with grafts of MSC and intrathecal injection of bFGF can promote tissue repair and functional recovery after spinal cord injury (SCI).

Materials and methods

Separation and culture of hMSCs

After our protocol had been determined and institutional review board approval was received, human MSCs were obtained from the iliac crest of patients during spinal fusion surgery using sterile syringes aspiration. All samples were collected after written informed consent was procured. MSCs were isolated by the non-selective flask adherent method following collection of the interphase fraction coat from a Ficoll gradient. When the cultures reach confluency, approximately after 2–3 weeks, the cells are harvested with 0.05% w/v trypsin and 0.02% w/v EDTA in phosphate-buffered saline (PBS; pH 7.4) for 5 min at 37 °C, replate and cultured once again for 2 weeks, then harvested. To identify and label cells derived from the cord blood, bromodeoxyuridine (BrdU, 3 ug/ml; Sigma, St. Louis, MO) was added to the medium for 3 days. Thereafter, the cells were subcultured in chambered slides and the BrdU incorporation was verified by BrdU immunocytochemical staining.

Spinal cord injury

A total of 30 male Sprague-Dawley rats (Daehan Hiolink, Chungbuk, Korea, body weight 200–300 g) were housed according to US national

institutes of health and USDA guidelines. All our animal experiments were approved by the institutional Animal Care and Use Committee of Yonsei University College of Medicine. All surgery was done under anesthesia with a combination (2 ml/kg) of ketamine (25 mg/ml), rompun (1.3 gm/ml), and acepromazine (0.25 mg/ml). A spinal cord moderate contusion lesion was made at the thoracic (T9) level using the New York University (NYU) weight-drop device. A metal rod 10 g in weight and 2.0 mm in diameter was dropped from a height of 25 mm onto the exposed spinal cord for contusion injury.

Transplantation of hMSCs and infusion of bFGF via subarachnoid space

Rats were assigned, without bias, to the control group (A, $n = 10$), the MSCs transplant group (B, $n = 10$), and the MSCs transplant and b-FGF group (C, $n = 10$). Control group animals were slowly injected 7 days after injury with 5 µl of PBS 1.2 mm deep on contusion epicenter using the glass micropipette injector system for 5 minutes. The MSCs transplantation groups were injected with 5 µl (5×10^5 cells) cell suspension at the same site as control group. The MSCs transplant and b-FGF group was injected with the same amount of cell suspension and infused with b-FGF (5 µl/day, 0.36 ng/µl) for 7 days after cell transplantation via intrathecal catheter. The control group and MSCs transplant group were infused with the same amount of phosphate buffered saline (PBS; GIBCO BRL), also for 7 days. Cyclosporin A (1 mg/100 gm) was injected daily from 2 days before transplantation to 8 weeks after transplantation.

Behavioral assessment after SCI

The hindlimb motor function was assessed by using the open-field BBB scoring system described by Basso *et al.* [1]. This scale measures hindlimb movements with a score of 0 indicating no spontaneous movement, with an increasing score being given for the use of individual joints, coordinated joint movement, coordinated limb movement, weight-bearing and so on to a maximum score of 21. The test was carried out 1 day postoperatively and once every week up to the eighth week after SCI. Behavioral testing was performed by two independent examiners who were kept blind to the rat's treatment status.

Histologic study

Cavity size evaluation after SCI

Eight weeks after transplantation, rats were perfused with 0.9% saline followed by a fixative solution of 4% paraformaldehyde. The T9 transplanted segment of the spinal cord was dissected and left on the same fixative solution at 4 °C. Segments 10 mm rostral and caudal of the injury site were then paraffin embedded. Longitudinal sections were collected from 20-mm-long spinal cord segments containing the injury and injection sites. Every 4th sections in each group were stained with Cresyl violate and the cavity size was measured with Metamorph image analysis system.

Immunohistochemistry

Forty micron sections were cut axially and collected in PBS at room temperature. For the immunologic studies, deparaffinized spinal cord sections were boiled in citrate buffer (pH 6.0) for 10 minutes in a microwave oven. Following blocking in normal serum, the sections were incubated with monoclonal antibodies (mAb) against human nuclear proteins (MAB 1281, dilution 1:50 in PBS, Chemicon, Temecula, CA) or bromodeoxyuridine (anti-BrdU, dilution 1:100 in PBS, Chemicon, Temecula, CA).

To identify cells co-expressing BrdU antibody with glial marker (GFAP) and neuronal marker (Neurofilament, MAP-2), we utilized fluorescence immunohistochemical staining techniques on all 3 groups. The secondary antibodies used in this study were sheep antibodies conjugated with Texas red (anti-sheep poly-Ab, 1:200; Vector Laboratories, Burlingame, CA) and mouse antibodies conjugated with fluorescein isothiocyanate (FITC) (anti-mouse mAb, 1:200; Vector Laboratories, Burlingame, CA). The sections were then washed, mounted and examined under a laser scanning confocal microscope equipped with a Bio-Rad MRC 1024 (argon and krypton) laser scanning confocal imaging system.

Statistical analysis

Comparisons of BBB scores between each group were made using an ANOVA test. Significance was accepted for $p < 0.05$.

Results

Characterization of MSC in vitro

Human MSCs isolated using the flask adherent method showed the typical polygonal shape of stromal cells. It took 3–4 weeks to obtain confluence after the first plating and the doubling time of these cells was 3–4 days. BMSC proliferated well in DMEM supplemented with 10% FBS without any added specific mitogens or growth factors. Immunocytochemistry for anti-CD105 antibody (human endothelial cell marker) revealed >90% of the positive cells at 3 passaged primate BMSC. Human specific anti-mitochondrial antibody also strongly labeled human MSCs. This antibody may be useful in subsequent transplantation studies (data was not shown).

BBB locomotion scores

The BBB scores of each group had an average of 5.8 points at post SCI week one. There were no differences in each group (p-value 1.00). There was no statistical difference until 5 weeks after injury between the groups. From

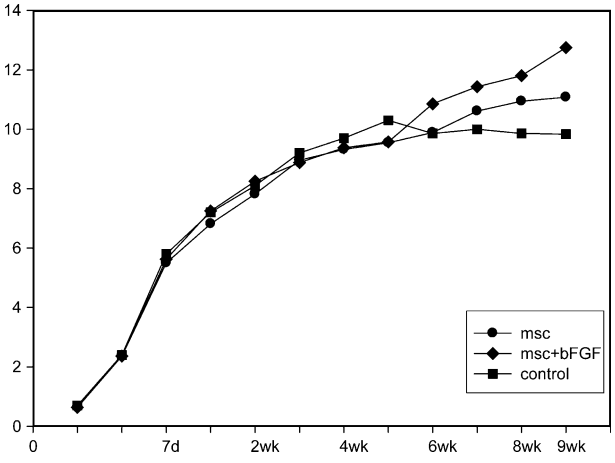

Fig. 1. BBB Scores of each group. Eight weeks after transplantation, the transplant group with MSCs and bFGF was more improved with regard to their BBB locomotion scores as compared to the other groups (one way ANOVA, $p < 0.05$)

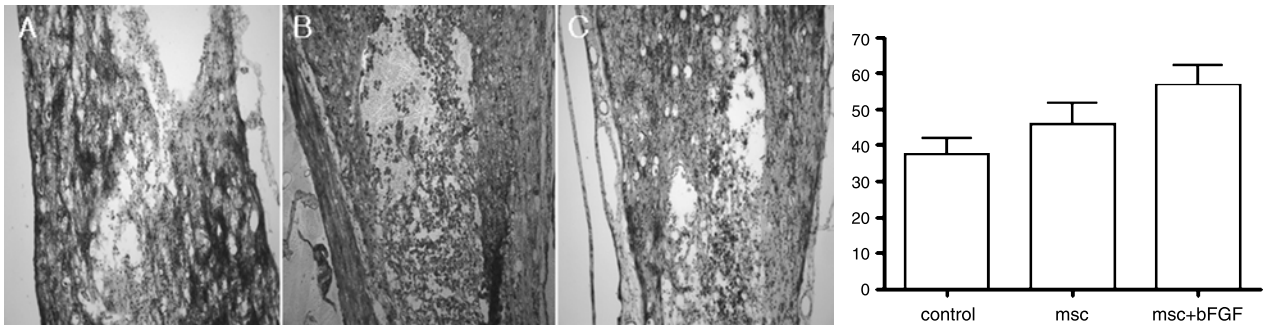

Fig. 2. Cavity sizes in each group at 9 weeks after injury. (*Left*) Cresyl-violet staining, ×100, (*Right*) volume of spinal tissue subtracted cavity %. (A) Control, (B) MSCs transplantation, (C) MSCs transplantation with bFGF infusion. The spinal cords of MSCs-injected rats had cavities much smaller than those of the control rats. The bFGF infusion group showed largest preserved spinal cord tissue among the three groups (One-way ANOVA test, $p < 0.05$)

6 weeks after injury (5 weeks after cell transplantation) the MSCs transplantation groups showed better functional recovery than the control group. At week 8 after transplantation, the BBB score were 9.8, 11.0, and 13.1 points for the A, B, and C groups, respectively (Fig. 1, One-way ANOVA test, $p < 0.05$). Thus, the MSCs transplantation group showed an early improvement compared to the control group, especially in the MSCs with b-FGF infusion group, which was dramatically improved in neurologic function compared to other groups ($p < 0.001$).

Cavity size comparison in each group and immunohistochemical results

For measurement of the cavity volume, 21 rats at 8 weeks post-transplantation were used. Every 4th long-

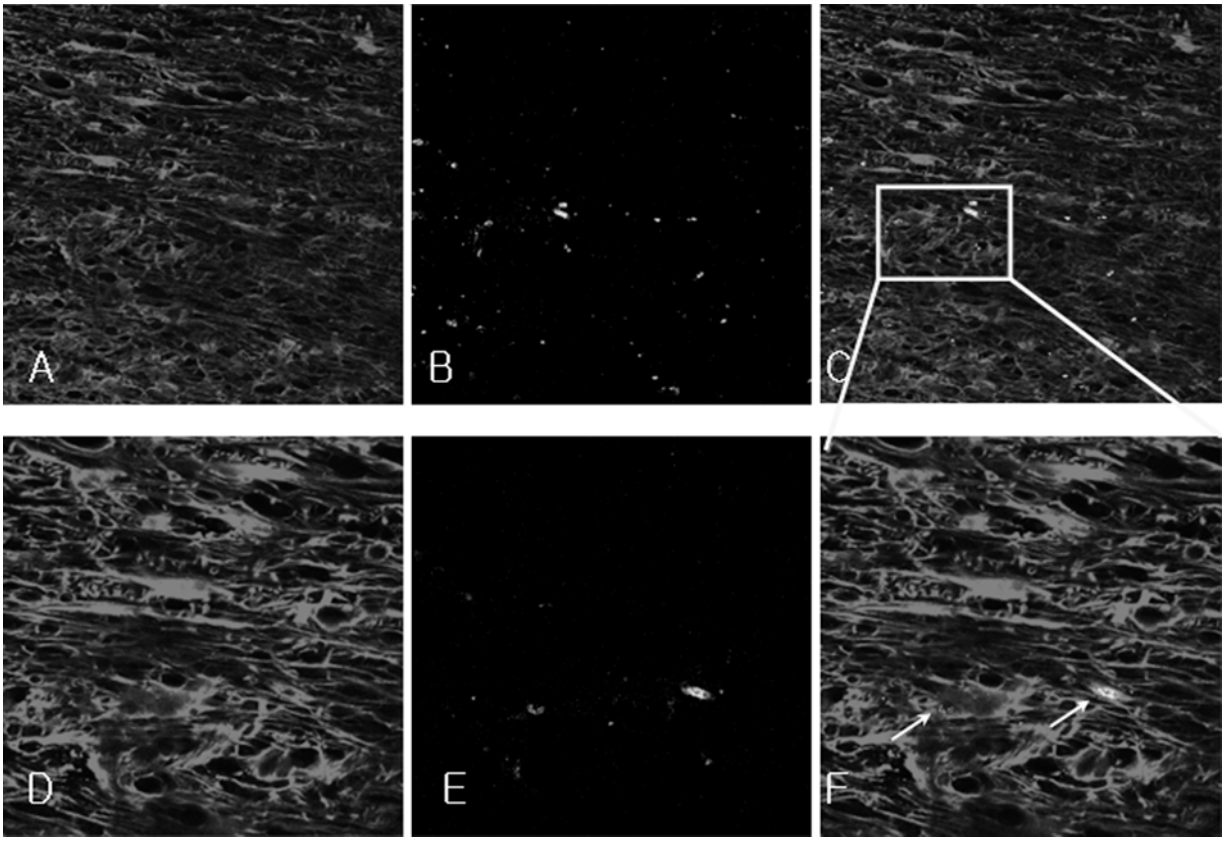

Fig. 3. Double immunofluorescence staining of BrdU (green) and GFAP (red). A, D: GFAP, B, E: BrdU, C, F: Merge (A, B, C: ×100, D, E, F: ×200). BrdU-GFAP positive cells were seen at MSCs injection site 8 weeks after transplantation

itudinal sections at an interval of 50 μm were stained with Cresyl violet. The volume (%) of spared spinal tissue was then calculated by Metamorph image analysis system. The spinal cords of MSCs-injected rats had cavities much smaller than those of the control rats. The bFGF infusion group showed largest preserved spinal cord tissue among the three groups (Fig. 2, $p < 0.05$). The BrdU positive transplanted cells were scattered around the cavity at injury epicenter area. The BrdU positive cell was also positive for anti-human mitochondrial antibody. The number of BrdU positive cells with or without bFGF infusion were calculated in 6 rats. In the bFGF infusion group, more transplanted cells survived than in the MSCs only transplant group (data was not shown). Double immunostaining with BrdU and GFAP antibodies showed that cells with BrdU and GFAP immunoreactivity were scattered in the spinal cord. Double immunostaining with NF and MAP-2 antibodies demonstrated that the BrdU-reactive cells did not express neural cells marker (Fig. 2).

Discussion

The present study demonstrated that human MSCs transplantation can improve locomotion with reduced cavity formation in the injured rat spinal cord. The infusion of bFGF via intrathecal route showed additional favorable effect to the damaged spinal cord. Some studies in rodents have demonstrated improved neurological recovery when MSCs were delivered following CNS injury [2–4]. However, the mechanisms that mediate these salutary effects remain speculative. In the present study small numbers of transplanted cells expressed glial marker (GFAP), but not neuronal markers. It is proposed that functional benefit observed in the MSCs-transplanted rats may not be due to the integration of MSCs into the injured tissue, but to the production of some trophic substances beneficial for the nervous tissue.

It was also reported that neurotrophic factors such as NT-3, BDNF, FGF, and NGF enhanced the regeneration of damaged axons and so helped recover neurological functions after CNS injury. Recently it was shown that bFGF delivery to injured rat spinal cord can promote functional recovery by neuroprotection and stimulation of endogenous cells [5]. In this study, we did not demonstrate an intrinsic mechanism of neurotrophic factor affecting neural repair. However, our experiment is consistent with growing literature that MSCs and neurotrophic factor promote tissue repair and functional recovery after spinal cord injury and suggest that MSCs transplantation and bFGF warrants investigation as a therapeutic intervention after spinal cord injury.

Conclusions

We have shown that MSCs transplantation and bFGF intrathecal infusion improve the neurological function and decrease post-injury cavitation in spinal cord injured rats. The growth factor may have neuroprotective or regenerative effects after spinal cord injury.

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References

1. Basso DM, Beattie MS, Bresnahan JC, Anderson DK, Faden AI, Gruner JA *et al* (1996) MASCIS evaluation of open field locomotor scores: effects of experience and teamwork on reliability. Multicenter Animal Spinal Cord Injury Study. J Neurotrauma 13: 343–359
2. Chopp M, Li Y (2002) Treatment of neural injury with marrow stromal cells. Lancet 1: 92–100
3. Chopp M, Zhang XH *et al* (2000) Spinal cord injury in rat: treatment with bone marrow stromal cell transplantation. Neuroreport 11(13): 3001–3005
4. Hofstetter CP, Schwarz EJ *et al* (2002) Marrow stromal cells form guiding strands in the injured spinal cord and promote recovery. PNAS 99(4): 2199–2204
5. Jimenez Hamann MC, Tator CH *et al* (2005) Injectable intrathecal delivery system for localized administration of EGF and FGF-2 to the injured rat spinal cord. Exp Neurol 194(1): 106–119
6. Ohta M, Suzuki Y *et al* (2004) Bone marrow stromal cells infused into the cerebrospinal fluid promote functional recovery on the injured rat spinal cord with reduced cavity formation. Exp Neurology 187: 266–278
7. Wu S, Suzuki Y *et al* (2003) Bone marrow stromal cells enhance differentiation of cocultured neurosphere cells and promote regeneration of injured spinal cord. J Neuro Res 72: 343–351

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Stem cell therapy in stroke: strategies in basic study and clinical application

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Summary

Stem cell therapies are an important strategy for the treatment of stroke. Bone marrow-derived stem cells (BMSCs) may promote structural and functional repair in several organs via stem cell plasticity. The tissue damage could stimulate the stem cells migration, and they track into the site of damage and then undergo differentiation. The plasticity functions of BMSCs in an injuries tissue are dependent on the specific signals present in the local environment of the damaged tissue. Recent studies have also identified the specific molecular signals, such as SDF-1/CXCR4, required for the interaction of BMSCs and damaged host tissues. This review summarizes the current understanding of how BMSCs reach and function in cerebral ischemic tissues.

Keywords: Stroke; stem cells; homing; therapy.

Introduction

Atherosclerosis of cerebral vessels leads to focal ischemic stroke and subsequent degeneration in the restricted central nervous system region with acute loss of neurons, astrocytes and oligodendrocytes [1]. This process finally results in tissue necrosis and possibly irreversible impairment of brain functions. In neurological disorders the aim of cell therapy is to replace, repair or enhance the biological function of damaged cells in order to restore brain function.

Several different types of stem cells, such as those from peripheral blood, bone marrow, and embryonic stem cells, have been successfully used to induce neurogenesis and functional recovery in various experimental models of ischemia [2, 3].

This functional recovery of the damaged brain is dependent on the response to specific signals present in the local ischemic tissue micro-environment. The beneficial effects are considered to be mediated by two factors: (1) increasing endogenous angiogenic, neurogenic and anti-apoptotic factors due to interactions between BMSCs and host brain parenchymal cells [2, 4, 5]; (2) differentiation of BMSCs themselves directly into both neuronal and endothelial cells that restore brain function [2]. Thus, BMSCs have neuroprotective effects not only directly, through their differentiation, but also through their ability to induce angiogenic, neurogenic and anti-apoptotic factors either by themselves or by interaction with host cells.

This review will focus on our recent studies on stem cell-based therapies for application in stroke patients, the possible mechanisms that may be involved in stem cell-based therapies, and how stem cells reach the site of cerebral ischemia and function there in the context of stem cell plasticity.

Granulocyte-colony stimulating factor (G-CSF) and stem-cell based therapy

Granulocyte colony-stimulating factor (G-CSF), a 20-kDa glycoprotein, is able to mobilize stem cells from bone marrow into the peripheral blood (PB) [6]. Recombinant G-CSF is also a common treatment after hematologic disease, or chemotherapy, when white blood cell counts tend to be dangerously low and there is a risk of infection [7]. G-CSF is also widely used to induce mobilization of blood precursors in different clinical settings such as chemotherapy-induced myelosuppression and peripheral blood stem cell recollection for autologous and allogeneic bone marrow transplantation [8].

We have recently demonstrated that G-CSF can enhance tissue regeneration and improve the survival rate after stroke by mobilizing BMSCs from bone marrow

into peripheral blood [9]. Our earlier study showed that subcutaneous injections of G-CSF, starting one day after cerebral ischemia and continuing for up to 5 days, promote BMSC migration to the injured brain and enhance neural repair in rats suffering from cerebral ischemia [9]. Infarction volume was markedly reduced, and there was also significant recovery of neurological dysfunction. G-CSF may enhance this process by increasing the number of circulating BMSCs, and their infiltration into the CNS. In addition, a sufficient number of BMSCs, mobilized by G-CSF, could home in on cerebral ischemic injuries to promote neuronal repair and recovery of brain function; this would provide a basis for the development of a non-invasive autologous therapy for cerebral ischemia. If G-CSF treatment can mobilize autologous BMSCs into circulation, enhance their translocation into the ischemic brain and thus significantly improve lesion repair, it represents an attractive strategy for the development of a clinically significant non-invasive stroke therapy. Our recent pilot clinical trial demonstrated that G-CSF could mobilize BMSCs in patients after acute stroke in a safe, feasible manner and provide a neurological outcome superior to conventional treatment (Shyu *et al.* manuscript submitted).

Chemotaxic factor of SDF-1/CXCR4

SDF-1 is a strong chemo-attractant for $CD34^+$ cells that express CXCR4, the receptor for SDF-1, and it plays an important role in BMSC trafficking between peripheral circulation and bone marrow [10]. SDF-1 regulates adhesion/chemotaxis of bone marrow hematopoietic progenitor cells through activation/regulation of specific integrin molecules [11–13]. Over-expression of SDF-1 in ischemic tissues has recently been found to enhance BMSC recruitment from PB and to induce neoangiogenesis [14, 15]. Since mobilized peripheral blood stem cells are increasingly used for clinical cell transplantation, it is becoming clear that proteolytic degradation of SDF-1 and CXCR4 on stem cells is an important step in stem cell release and homing [16].

Since SDF-1 receptors are present on bone marrow stem cells [17], up-regulation of SDF-1 in the local ischemic damage after injury [18–20] may be related to homing and engraftment of stem cell to the injured tissue. Hill *et al.* [21] recently demonstrated that up-regulation of SDF-1 was associated with endothelial cells when GFP-bone marrow transplanted mice underwent temporary middle cerebral artery occlusion (MCAo). We hypothesize that SDF-1 is up-regulated in ischemic tissues and that ischemia-associated hypoxia causes an imbalance between plasma and bone marrow SDF-1 concentration, resulting in the transient establishment of an SDF-1 gradient that favors stem cell translocation into ischemic tissue, thereby enhancing angiogenesis and functional recovery.

Function of stem cells in ischemic brain

It is possible that BMSCs migrating to the ischemic hemisphere create local chemical gradients and/or localized chemokine accumulation, dictating a directional response in endothelial, neuronal and glial progenitor cells [14]. For example, SDF-1 might also stimulate host endothelium progenitor cell (EPC) differentiation from pre-existing blood vessels and/or host EPCs derived from bone marrow [22]. In the ideal transplantation scenario, stem cells implanted directly into or around the damaged area would differentiate in situ into those original host cells that have died. The optimum strategy would probably be to combine transplantation of neural stem cells (NSCs) close to the damaged area with stimulation of neurogenesis from endogenous NSCs forming a ''new neuron network''.

The results of our recent study suggested that mobilized EPCs contributed to ''collateral circulation'', and could even ''line-up'' and ''build'' new vessels in the ischemic brain [23].

Conclusion

Definitely, cell therapy may serve as a future restorative therapy for stroke. Further studies are necessary to examine whether stem cells can have a therapeutic role as, supportive cells, a sole treatment and/or as vehicles of gene delivery; and to what extent these cells are capable of neuronal remodeling. Moreover, it remains to be shown how transplanted cells are integrated into neuronal circuits and promote functional recovery, and whether grafts survive for long periods of time.

References

1. Blau HM, Brazelton TR, Weimann JM (2001) The evolving concept of a stem cell: entity or function? Cell 105: 829–841
2. Chen J, Li Y, Wang L, Zhang Z, Lu D, Lu M, Chopp M (2001) Therapeutic benefit of intravenous administration of bone marrow stromal cells after cerebral ischemia in rats. Stroke 32: 1005–1011
3. Li Y, Chen J, Chen XG, Wang L, Gautam SC, Xu YX, Katakowski M, Zhang LJ, Lu M, Janakiraman N, Chopp M (2002) Human marrow stromal cell therapy for stroke in rat: neurotrophins and functional recovery. Neurology 59: 514–523

4. Sun Y, Jin K, Xie L, Childs J, Mao XO, Logvinova A, Greenberg DA (2003) VEGF-induced neuroprotection, neurogenesis, and angiogenesis after focal cerebral ischemia. J Clin Invest 111: 1843–1851
5. Lu D, Mahmood A, Wang L, Li Y, Lu M, Chopp M (2001) Adult bone marrow stromal cells administered intravenously to rats after traumatic brain injury migrate into brain and improve neurological outcome. Neuroreport 12: 559–563
6. Demetri GD, Griffin JD (1991) Granulocyte colony-stimulating factor and its receptor. Blood 78: 2791–2808
7. Wong SF, Chan HO (2005) Effects of a formulary change from granulocyte colony-stimulating factor to granulocyte-macrophage colony-stimulating factor on outcomes in patients treated with myelosuppressive chemotherapy. Pharmacotherapy 25: 372–378
8. Law P, Lane TA (2002) Mobilization of allogeneic peripheral blood progenitor cells. Cancer Treat Res 110: 51–77
9. Shyu WC, Lin SZ, Yang HI, Tzeng YS, Pang CY, Yen PS, Li H (2004) Functional recovery of stroke rats induced by granulocyte colony-stimulating factor-stimulated stem cells. Circulation 110: 1847–1854
10. Petit I, Szyper-Kravitz M, Nagler A, Lahav M, Peled A, Habler L, Ponomaryov T, Taichman RS, Arenzana-Seisdedos F, Fujii N, Sandbank J, Zipori D, Lapidot T (2002) G-CSF induces stem cell mobilization by decreasing bone marrow SDF-1 and up-regulating CXCR4. Nat Immunol 3: 687–694
11. Wright DE, Bowman EP, Wagers AJ, Butcher EC, Weissman IL (2002) Hematopoietic stem cells are uniquely selective in their migratory response to chemokines. J Exp Med 195: 1145–1154
12. Peled A, Kollet O, Ponomaryov T, Petit I, Franitza S, Grabovsky V, Slav MM, Nagler A, Lider O, Alon R, Zipori D, Lapidot T (2000) The chemokine SDF-1 activates the integrins LFA-1, VLA-4, and VLA-5 on immature human CD34(+) cells: role in transendothelial/stromal migration and engraftment of NOD/SCID mice. Blood 95: 3289–3296
13. Jo DY, Rafii S, Hamada T, Moore MA (2000) Chemotaxis of primitive hematopoietic cells in response to stromal cell-derived factor-1. J Clin Invest 105: 101–111
14. Yamaguchi J, Kusano KF, Masuo O, Kawamoto A, Silver M, Murasawa S, Bosch-Marce M, Masuda H, Losordo DW, Isner JM, Asahara T (2003) Stromal cell-derived factor-1 effects on ex vivo expanded endothelial progenitor cell recruitment for ischemic neovascularization. Circulation 107: 1322–1328
15. Hiasa K, Ishibashi M, Ohtani K, Inoue S, Zhao Q, Kitamoto S, Sata M, Ichiki T, Takeshita A, Egashira K (2004) Gene transfer of stromal cell-derived factor-1alpha enhances ischemic vasculogenesis and angiogenesis via vascular endothelial growth factor/endothelial nitric oxide synthase-related pathway: next-generation chemokine therapy for therapeutic neovascularization. Circulation 109: 2454–2461
16. Levesque JP, Hendy J, Takamatsu Y, Simmons PJ, Bendall LJ (2003) Disruption of the CXCR4/CXCL12 chemotactic interaction during hematopoietic stem cell mobilization induced by GCSF or cyclophosphamide. J Clin Invest 111: 187–196
17. Rodgers KE, Xiong S, Steer R, diZerega GS (2000) Effect of angiotensin II on hematopoietic progenitor cell proliferation. Stem Cells 18: 287–294
18. Yamagishi H, Kim S, Nishikimi T, Takeuchi K, Takeda T (1993) Contribution of cardiac renin-angiotensin system to ventricular remodelling in myocardial-infarcted rats. J Mol Cell Cardiol 25: 1369–1380
19. Sawa H, Kawaguchi H, Mochizuki N, Endo Y, Kudo T, Tokuchi F, Fijioka Y, Nagashima K, Kitabatake A (1994) Distribution of angiotensinogen in diseased human hearts. Mol Cell Biochem 132: 15–23
20. Hirsch AT, Talsness CE, Schunkert H, Paul M, Dzau VJ (1991) Tissue-specific activation of cardiac angiotensin converting enzyme in experimental heart failure. Circ Res 69: 475–482
21. Hill WD, Hess DC, Martin-Studdard A, Carothers JJ, Zheng J, Hale D, Maeda M, Fagan SC, Carroll JE, Conway SJ (2004) SDF-1 (CXCL12) is upregulated in the ischemic penumbra following stroke: association with bone marrow cell homing to injury. J Neuropathol Exp Neurol 63: 84–96
22. Chen J, Zhang ZG, Li Y, Wang L, Xu YX, Gautam SC, Lu M, Zhu Z, Chopp M (2003) Intravenous administration of human bone marrow stromal cells induces angiogenesis in the ischemic boundary zone after stroke in rats. Circ Res 92: 692–699
23. Buschmann IR, Hossmann KA (2005) Letter regarding article by Shyu *et al*, ''functional recovery of stroke rats induced by granulocyte colony-stimulating factor-stimulated stem cells''. Circulation 111: e297–e298; author reply e297–e298

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Neural prosthesis in the wake of nanotechnology: controlled growth of neurons using surface nanostructures

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Summary

Neural prosthesis has been successfully applied to patients with motional or sensory disabilities for clinical purpose. To enhance the performance of the neural prosthetic device, the electrodes for the biosignal recording or electrical stimulation should be located in closer proximity to target neurons than they are now. Instead of revising the prior implanting surgery to improve the electrical contact of neurons, we propose a technique that can bring the neurons closer to the electrode sites. A new method is investigated that can control the direction of neural cell growth using surface nanostructures. We successfully guide the neurons to the position of the microelectrodes by providing a surface topographical cue presented by the surface nanostructure on a photoresponsive polymer material. Because the surface structure formed by laser holography is reversible and repeatable, the geometrical positioning of the neurons to microelectrodes can be adjusted by applying laser treatment during the surgery for the purpose of improving the performance of neural prosthetic device.

Keywords: Photoresponsive polymer; surface structure; neural cell guide; growth control; neural prosthesis.

Introduction

Neural prosthesis is a technology which rehabilitates a patient with motional or sensory disability by electrical recording or stimulation of the neurons [2]. The neural prosthesis has become an important therapeutic option for these disabilities because transplantation and stem cell approaches for the neural cell are promising, but still distant. Significant progress has been made in several areas of neural prosthesis. The cochlear implant system restores the auditory sense in the deaf [4]. The artificial retina system stimulates the remained retinal neural cells in patients with degenerated photoreceptors to restore vision [8]. The cortical prosthetic device is proposed to monitor and stimulate the motor cortex for quadriplegic patients due to cervical injury and amyotrophic lateral sclerosis [7]. Functional electrical stimulation is also promising for patients with neurogenic bladder, paraplegia due to lumbar injury and so on [10]. Microelectrodes in these devices play a crucial role in stimulating and recording neural signals for monitoring and controlling the activities of the nervous system. To record the biosignals and stimulate the neurons effectively with high resolution, the electrodes have to maintain contact with the targeted neuronal cells closely enough to focus the electrical current onto the target cells. The electrode surface needs to be within 100 nm of the nerve cell in order to obtain a reasonable signal to noise ratio [5]. However, in almost all prosthetic devices, the relative position of electrodes with respect to target neurons is determined at the moment of the operation. Correct positioning of the electrode with micro and nanoscale precision is not possible with conventional surgery. Moreover, once the device is implanted into the body of the patient, the position cannot be adjusted without revision of the previous implantation surgery. In an approach of enhancing the interfacing electrical activity [1], a semiconductor fabrication technique with silicon, silicon nitride, and gold was used to provide a substrate to align neurons by reaction to the topography. This approach succeeded in guiding the neurons by providing micro or nano structure on the surface of the devices.

Nevertheless, the limitation of such approach is that the topography in the substrate is fixed after fabrication, so modifying the physical structure to adjust the position of the neurons after surgery is not possible. A material with dynamically changeable properties would open a

new stage of adjusting the cells to the electrodes by controlling the growth of neurons. Photofabrication with laser holography provides unique advantages over conventional techniques, including being a one-step process without complicated procedures, and allowing patterning without a photomask, easy control of depth and width, noncontact optical fabrication, and the superimposition and reversibility of patterns [3, 6]. Micro and nanoscale grooved structure can be generated with laser holographic fabrication. The primary hippocampal neurons are known as changing directions of neurites growth on the microgrooved structure [9]. This implies that the hippocampal neurons can be guided onto the target electrode by the contact guidance. By applying this photofabrication technology to neural prosthetic devices, it is expected that the relative position of neurons could be improved without surgery after insertion of the device.

Materials and methods

Holographic photoresponsive polymer

Azobenzene copolymer, poly [(methylmethacrylate)-co-(disperse red 1 acrylate)] (57042-7, Sigma Aldrich) was used as a holographic photoresponsive polymer. It was dissolved in tetrahydrofuran at a concentration of 5% (w/w). The polymer film was formed by spin coating on a cover glass with a thickness of about 1 μm. The coated polymer was dried for 6 hours at 70 °C to remove the solvent.

Surface fabrication and laser holography

In order to form a holographic SRG, we used a 488-nm Ar^+ ion laser and the classic Lloyd's mirror setup (Fig. 1). Light from the laser was expanded by a beam expander at an appropriate range and polarized. We formed an interference pattern by the superposition of two beams. One came directly from the laser and the other was reflected from a mirror. The incident beam from the laser was linearly polarized at an angle of $+45°$ while the reflected beam from the mirror had an angle of $-45°$ with respect to the substrate normal. These two orthogonal beams exhibited polarization modulation on the polymer surface resulting in molecular migration to form regular sinusoidal SRG. The intensity of Ar^+ ion laser was about 300 mW/cm^2. The width of grooves was determined by the combination angle between the two beams, and the depth by the duration of laser irradiation. The formation of the grating was monitored in real time by probing with a He–Ne laser (wavelength of 633 nm) onto the inscribed region. The probe beam was linearly polarized at 45° to the axis of grating and did not influence the fabrication process.

Cell culture

Primary hippocampal neurons were prepared from embryonic day 18 Sprague-Dawley rats as described previously [15]. The dissociated neurons were placed in modified Eagle's medium supplemented with 20% glucose, 1 mM sodium pyruvate, 2 mM L-glutamine, and penicillin-streptomycin (Invitrogen) for 3 hours, and grown in neurobasal medium supplemented with B27 and 0.5 mM L-glutamine. To reduce glial proliferation, we treated the neurons with Ara-C after 3 days. Once a week, we removed half the volume of medium and replaced it with fresh maintenance medium. To sterilize the polymer for culturing neurons, the prepared polymers were dipped into 70% (v/v) ethanol in water and rinsed three times with sterilized water. Prior to cell seeding, cover glasses were treated with poly-D-lysine coating to enhance the adhesion of the neuronal cells on the polymer substrate.

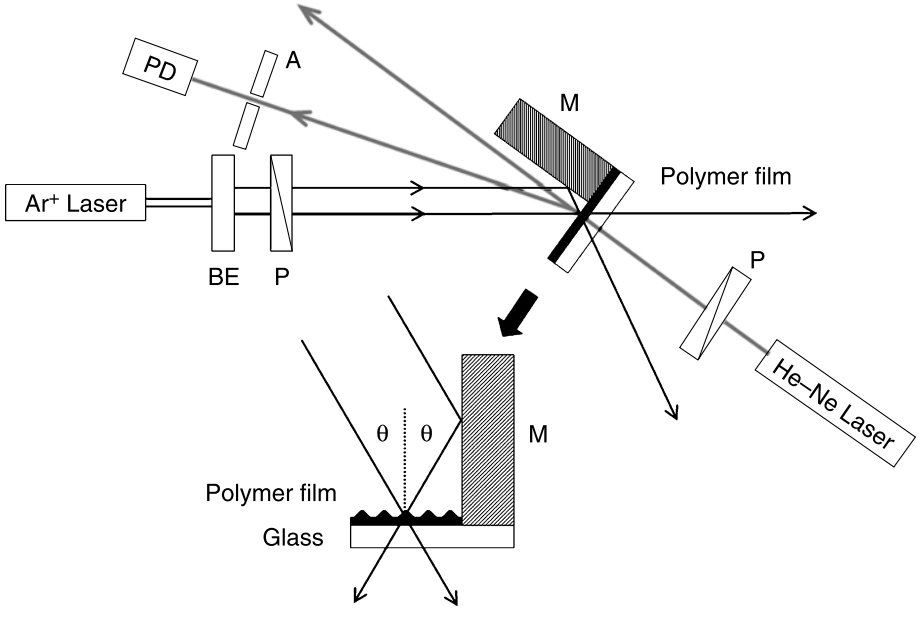

Fig. 1. Schematic view of the optic setup for SRG formation. Two orthogonal beams interfered on the surface of the polymer to form the groove structure. The period of the grating pattern depended on the combination angle θ. (*PD* Photo detector, *BE* beam expander, *P* polarizer, *M* mirror, *A* aperture)

Analysis of cell morphology

After inscribing SRG on the polymers, the exposed surfaces were investigated with a scanning electron microscope (SEM, XL30FEG, Philips) and an atomic force microscope (AFM, XE-150, PSI) in contact mode. Cell morphology was analyzed with a phase- and differential-contrast microscope. Rat hippocampal neurons were washed with phosphate-buffered saline (PBS) and fixed with 4% (v/v) paraformaldehyde for 10 min at room temperature. After fixation, cells were gently washed with PBS and dehydrated in a series of ethanol solutions (70, 80, 90, then 100% (v/v), each for 10 min) to ensure total dehydration. The samples were desiccated overnight, sputtered with gold, and analyzed by SEM.

Results and discussion

Cell viability

Primary hippocampal neurons were proliferated on poly-D-lysine coated photoresponsive polymer. The viability of neural cells on the polymer was investigated by optical microscopy. The morphology of the cells indicated that they were healthy, lacking any symptoms of cell deterioration such as retracted or beaded neurites, swollen somata, or detachment from the polymer surface. The cultured cells survived for over 6 weeks, during which time the polymer did not degenerate.

Neurons guiding with photoresponsive polymer

The morphology of neurons on the surface patterned with grooves was observed using both optical microscopy and SEM. Figure 2a shows a neuron cultured on SRG, whose neurites grew out from the cell body perpendicular to the grooves formed by laser holography. In Fig. 2b, neurites were also aligned in perpendicular direction, revealing that neurons have a strong tendency to grow in perpendicular direction in the grooved surface. The repeating microgrooves provided a continuous topographical cue to the neuronal behavior, making the neurites grow perpendicular to the grooves.

Figure 3a shows the localized topographic effect on the growth of neuronal process. When the neurites of a neuron with its cell body outside of the grooved region grew into the microfabricated region, the neurites adjusted their trajectories to the direction perpendicular

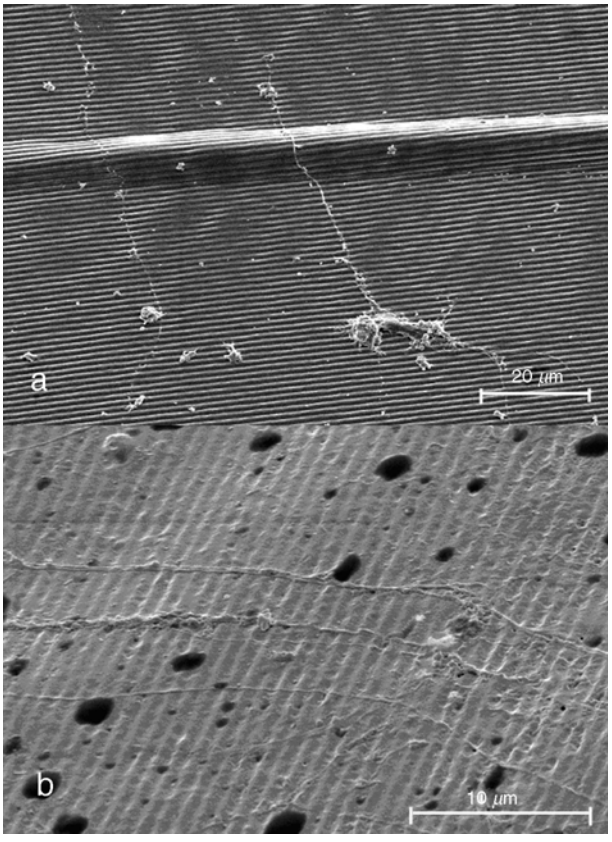

Fig. 2. SEM image of rat hippocampal neurons attached on SRG (1.4 μm wide, 400 nm deep), clearly showing a neurite growing out from a cell body perpendicular to the direction of microgrooves (a). The directions of the neurites were controlled by the surface topography, aligned in perpendicular direction to the grooves (b)

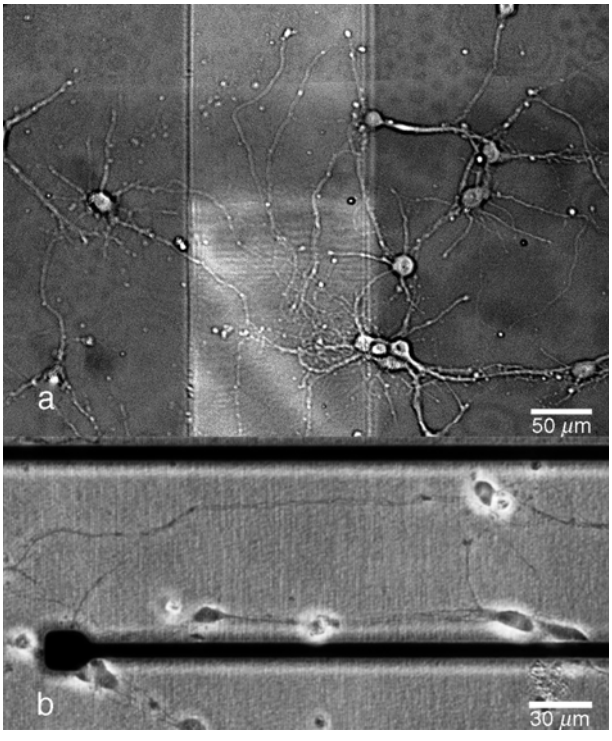

Fig. 3. Optical microscopy image of rat hippocampal neurons after 6 days in culture: (a) SRG (1.2 μm wide, 600 nm deep) is running horizontally in the middle light region. Neurites extending into the grooved region tended to grow perpendicular to the SRG. (b) Neurons were guided to grow towards an electrode site by laser-treated surface topography

to the grooves. This observation further supports that the direction of growth of living neurons can be controlled using photofabrication with laser holography. Figure 3b demonstrates guiding neurons to the site of recording and stimulating microelectrode array. Black lines are gold line insulated with an insulating layer to transmit the current to the cells, and the black square on the end of gold line is a recording and stimulating site which is not insulated. Photoresponsive polymer was coated on the insulation layer of the microelectrode array. To make a contact between a microelectrode site and a neuron, we made the laser-induced surface gratings on the polymer. The neurons responded to the microtopography and were guided toward the site of electrode.

Conclusion

Interfacing nerve or sense cells with microelectrodes is important for the successful performance of neural prosthetic devices. Micro and nano surface structure generated by laser holographic method was applied to guiding neural cells. On the laser-treated region, rat hippocampal neurons showed a strong tendency of growing in a perpendicular direction to the grooved surface structure. We succeeded in guiding the neural cells toward the site of microelectrode. Our experiments indicate that laser holographic fabrication on azobenzene copolymer is a promising technique to enhance the electrical interface between neurons and microelectrodes. This could be used to improve the performance of neural prosthetic device after implanting the device in a noninvasive manner.

References

1. Breckenridge L, Clark P, Connolly P, Curtis ASG, Dow JAT, Wilson R, Lind R, Wilkinson CDW (1992) Artificially induced nerve cell patterning or real neural networks Synthetic microstructures in biological research. Plenum, New York, pp 201–206
2. Chapin JK, Moxon KA (2001) Neural prostheses for restoration of sensory and motor function. CRC Press, Boca Raton
3. Chun C, Kim M, Vak D, Kim DY (2003) A novel azobenzene-based amorphous molecular material with a spiro linked bifluorene. J Mater Chem 13: 2904–2909
4. Clark GM (1998) Research advances for cochlear implants. Auris Nasus Larynx 25(1): 73–87
5. Curtis A, Riehle M (2001) Tissue engineering: the biophysical background. Phys Med Biol 46: R47–R65
6. Jiang XL, Li L, Kumar J, Kim DY, Tripathy SK (1998) Unusual polarization dependent optical erasure of surface relief gratings on azobenzene polymer films. Appl Phys Lett 72: 2502–2504
7. Lauer RT, Peckham PH, Kilgore KL, Heetderks WJ (2000) Applications of cortical signals to neuroprosthetic control: a critical review. IEEE Trans Rehabil Eng 8(2): 205–208
8. Margalit E, Maia M, Weiland JD, Greenberg RJ, Fujii GY, Torres G, Piyathaisere DV, O'Hearn TM, Liu W, Lazzi G, Dagnelie G, Scribner DA, de Juan E Jr, Humayun MS (2002) Retinal prosthesis for the blind. Surv Ophthalmol 47(4): 335–356
9. Rajnicek M, Britland S, McCaig CD (1997) Contact guidance of CNS neurites on grooved quartz: influence of groove dimensions, neuronal age and cell type. J Cell Sci 110: 2905–2913
10. Peckham PH, Knutson JS (2005) Functional electrical stimulation for neuromuscular applications. Ann Rev Biomed Eng 7: 327–360

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A new and simple transection knife for study of neurodegeneration and neuroregeneration in animal model

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Summary

Background. The purpose of this study was to design and make a simple, inexpensive brain knife that could produce consistent results following transection in animal model.

Materials and methods. After testing various materials including commercially available products, microelectrode recording needles as used in deep brain stimulation (DBS) surgery were selected as ideal candidates. They were modified to serve as type of wire-knife for the purposes of study. For this study, the major pathway for dopaminergic neuron from substantia nigra to striatum was selected for transection. A total of 40 Sprague-Dawley rats were assigned to 8 groups; normal, 1–4, 6, 8, and 10 weeks post-transection. Degree of cell death was determined and surviving neurons were counted by means of fluorescent microscopic examination, immunohistochemistry involving tyrosine hydroxylase (TH)-immunoreactive staining, and mapping to verify complete transection.

Results. Compared to control, percentage of remaining neurons in each group was 61.3, 36.8, 29.9, 5.1, 5.9, 7.0%, respectively. Completeness of lesion was correlated with the absence of TH-immunoreactivity in the striatum.

Conclusion. Our model seems to provide complete cell death in early period after transection with consistent results. Thus, this type of brain knife can be very handy, without any extra cost, in any research model involving transection of fiber bundle for studies on neurodegeneration and neuroregeneration.

Keywords: Knife; electrode; transection; substantia nigra; cell death; degeneration.

Introduction

Various types of injury to the central nervous system, mechanical, chemical, inflammatory or ischemic, cause varying degrees of degeneration of damaged neurons [18]. The degree of cell death whose outflow tract is injured may be related to the nature of injury, the proportion of axons within the tract that are damaged, and the distance of injury to the nucleus [5]. However, previous studies have indicated that much more time is required, at least 10–12 weeks, for cell death to take place in experimental models of mechanical transection involving the optic or nigrostriatal pathway [18, 21]. This may be due not only to location or type of injury but the extent of injury, where partial injury may provoke slow and incomplete degeneration of neurons involved. This type of model may be ideal for studying the nature of a slow progressive course of degenerative process. However, it would be very appealing for the monitoring of therapeutic measures if such process can be obtained at short term with complete lesion.

Nigrostriatal pathway has been lesioned surgically [18], electrolytically [3] and chemically using both 6-hydroxydopamine(6-OHDA) [7, 23, 26, 31] and methyl-4-phenyl-1,2,3,6-tetra-hydro-pyridine [9, 13]. However, inconsistent results have been reported with regard to extent of lesion and time course of cell death. Also, different methods for lesioning the nigrostriatal tract have been reported to lead to different degrees and rates of dopaminergic neuronal cell death. Previous studies have shown that after a mechanical transection of the medial forebrain bundle (MFB), about 50% of SN dopaminergic neurons survive; reported survival rates being 44% at 18 days [17] and 50% at 19 days after transection using an commercialized extruding wire knife, 60% survival 56 days after partial hemitransection of the midbrain, and 52% survival at 15 days [16] and 31–44% survival at 14 days [30] after hemitransection. However, these commercialized available knifes are quite expensive and do not last long. Thus, it was intended in this study to establish a mechanical transection injury model where a more complete lesion can be obtained in a short period of time

to provide an effective, simple and inexpensive model to be used for studies of degeneration and regeneration.

Material and methods

Operations

A total of 40 female Sprague-Dawley rats weighing between 200 and 250 g were anaesthetized using 1.5 cc mixture of ketamine (62.5 mg/kg) and xylazine (3.25 mg/kg) administered intraperitoneally. Additional dosage of anesthetics was given according to the depth of anesthesia. The animals were then fixed into a stereotaxic frame (David Kopf) with the incisor bar set at 3.3 mm below the interaural line. A midline incision was made and the periosteum cleared from the cranium before the tip of the operating instrument was referenced against the bregma. The relevant piece of skull was removed using a dental drill before a second reference was made against the dura [21].

Retrograde tracer injections

Bilateral intrastriatal injections were made in 80 of the animals seven days before the nigrostriatal transection using a Hamilton syringe (Precision Sampling Corporation). Twelve different coordinates at six different tracts of each striatum according to Paxinos and Watson atlas [26] were chosen to level the whole striatum, and each of these were 1) 1.6 mm anterior to bregma (AP: 1.6), 1.7 mm from midline(L: 1.7), and 4.4 mm & 5.8 mm from cortex (D: −4.4, −5.8); 2) AP: 1.3, L: 3.0, D: −4.2, −6.4; 3) AP: 0.3, L: 2.3, D: −3.7, −7; 4) AP: 0.1, L: 4.0, D: −4.4, −6.8; 5) 1.2 mm posterior to bregma(AP: −1.2), 4.5 mm lateral to midline (L: 4.0), and 5.0 mm & 7.0 mm from cortex (D: −5, −7); and 6) AP: −2.8, L: 5.0, D: −6, −6.6 (Fig. 1). The tip of the syringe was lowered vertically according to these stereotactic coordinates and retrograde fluorescent tracer DiI (1,1′-dioctadecyl-3,3,3′,3′-tetramethyl-indocarbocyanine perchlorate) was then injected (2 µl at each tract and 1 µl at last tract) and the syringe was left in situ for 2 min before being withdrawn.

Nigrostriatal transection

The right nigrostriatal tract of 45 animals was transected in the MFB using our custom-designed, modified small wire knife. It is similar to the wire knife developed by Scouten *et al.* [34] (Fig. 1). It is mainly made of platinum-tongsten steel and has a memory effect so that it would be kept straight within the guide-canula, but will have circular configuration when it is pushed-out from the canula. It is 100-µm thick and 3-mm wide by 3-mm high. The tip of the knife with the outer canula was lowered vertically from a point 3.6 mm posterior to and 3.0 mm right of the bregma, and to 6.0 mm below the dura before the wire was extruded. It was intended to transect MFB which contains most of the nigrostriatal fibers corresponding to 1 mm rostral to the tip of SN. When the knife is extruded from the canula, it forms a smooth curve in the coronal plane, reaching 3.0 mm medial and about 3.0 mm from the tip of the canula. The knife is then withdrawn vertically by 2.5 mm. Thereafter the blade was retracted before again being extruded and lowered by 2.5 mm. Thus, the tract was cut twice before the wire was finally retracted and the knife removed.

Immunohistochemistry

All experimental animals, including the control ones, were deeply reanesthetized with a toxic dose of the same anesthetics according to time protocol and transcardially perfused with 75 ml of cold PBS and 250 ml of cold 4% paraformaldehyde in 0.1 M phosphate buffer solution (PBS at pH 7.4) at 4 °C over 20 min. The brains were then removed and postfixed for 2 h in the same solution before being cryoprotected in PBS containing 30% sucrose overnight at 4 °C. Coronal sections of 25 µm thickness were cut on a freezing microtome from brain immobilized in standardized position according to Paxino–Watson atlas [26]. Section containing rostral pole of SNpc (neuronal group A9 [6]) was carefully determined first (corresponding to 4.0 mm caudal to bregma, named section "0", and most caudal section being 1.6 mm from section "0"). Every seventh section through the nigral complex was mounted in water-based fluoromount-G (Fisher Scientific) on uncoated glass slides, analysed for the number of DiI-labeled SN neurons, and photographed. Sections were then incubated in a free floating state at room temperature (if taken from slides after counting DiI labelled neurons) or washed 3 × 10 min (if sections were in free floating state) with TBS containing 0.25% Triton X. Sections were then blocked in PBS containing 5% goat serum and 0.2% Triton X-100 for 30 min before being transferred to a I: 40,000 diluted solution of mouse monoclonal anti-tyrosine hydroxlase (anti-TH) antibody (Chemical International Inc.) in which they were incubated in TBS/serum (1%)/Triton X-100 for 2 h at room

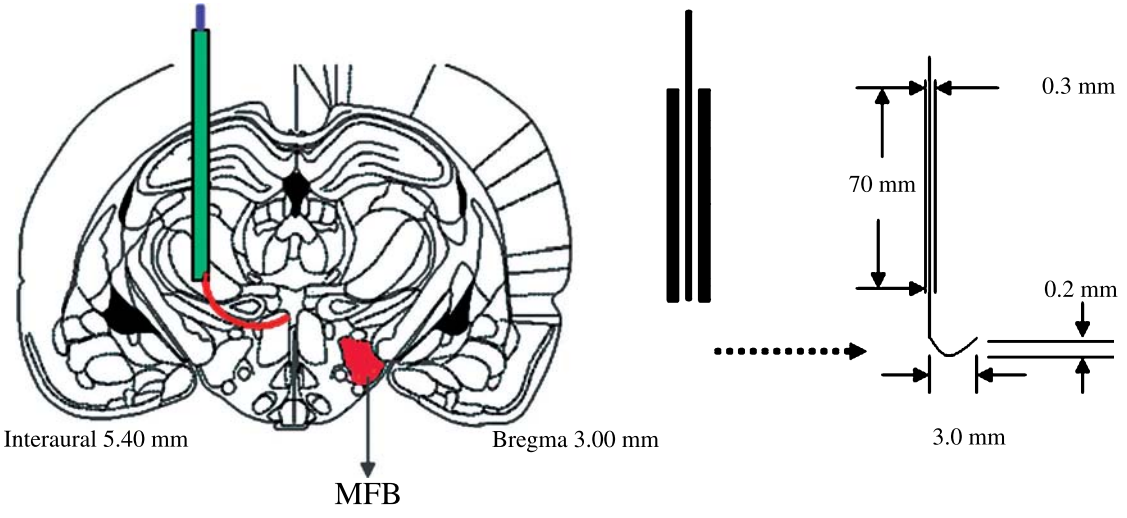

Fig. 1. Transection of MFB by custom-designed wire knife. It is 100 µm thick, 3 mm long, 3 mm high, forms a curved shape when it is extruded into target region. Two vertical cuttings are made at target coordinates of (*L*) 3.0 mm, (*AP*) −3.6 mm, (*DV*) −6.0 mm with tool bar set at −3.3 mm. It is done by mediolateral plane movement and is slipped back into guidance carrier after cutting

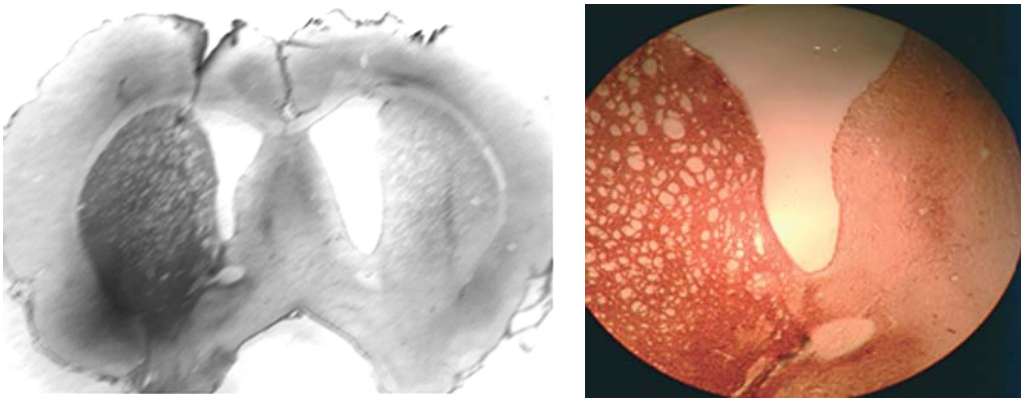

Fig. 2. Completeness of transection is demonstrated by absence of TH(−) immunostaining (*right*) compared to control side (*left*)

temperature followed by 16 h at 4 °C. Visualization of antibody binding was with a biotinylated goat anti-mouse immunoglobulin antibody (Vector Labs) in TBS/serum at 1:200 for 1.5 h followed by 1.5 h with avidine biotin I complex (ABC Elite, Vector Labs) in TBS. Peroxidase activity was developed in 0.04% 3,3-diaminobenzidine tetrahydrochloride/0.06% $NiCl_2$/0.02% H_2O_2 in Tris HCl. Sections were finally washed 3×10 min in PBS and mounted on glass slides subbed with 0.2% gelatin, in glycerol gelatin, air dried, incubated for 30 seconds in 0.005% OsO_4, dehydrated in ethanol, cleared in xylene, and coverslipped in Permount.

Mounted sections were examined using a fluorescent microscope (Leitz) and number of TH-immunopositive SNpc neurons as defined by Bjorklund and Lindvall having a maximal cell body diameter greater than 10 µm on both transected and control sides were counted at 250× magnification and mapped using NIH Image software for survival and location of cell death according to time. Size of cell body was also measured. After analysis and photography, sections were rehydrated and stained with cresyl violet.

Total number of SNpc neurons were calculated according to Abercrombie formula for correction of split-cell counting errors where $N = n[t/t(t + d)]$ (N = total number of cells; n = number of cell counted; t = section thickness; and d = cell diameter) [1]. Also, counts were expressed as a percentage of the number of neurons labelled on the lesioned side compared with the number on the control side for each animal.

Results

Animals were sacrificed one to 16 weeks after mechanical transection of the MFB. Coronal sectioned brains were processed for immunohistochemistry against TH. Completeness of transection of MFB was evidenced by absence of TH-(+) fibers in the striatum (Fig. 2). Borders used to define the SNpc (A9) were first outlined by Bjorklund [6] and later adopted by Hagg and Varon [11].

Comparison of DiI, TH-(+) labeled, and cresyl violet stained neurons in control animals

In 5 control animals, the total number DiI (+) and TH-(+) labeled neurons in both sides of SNpc were counted to see whether most neurons in SNpc were labeled compared to all neurons irrespective of size and phenotype expression that were stained exclusively in cresyl violet. Total number of TH-(+) neurons in SNpc of the non-lesioned side of animals was not significantly different from that in control animals [3687 ± 88 (mean ± SEM) vs. 3927 ± 86; Abercrombi corrected; Mann-Whitney U test]. The total number of DiI (+), TH-(+), and cresyl violet stained neurons in each SNpc of control animals were 3222 ± 86, 3369 ± 84, and 3663 ± 82, respectively. This indicates that the number of TH-(+) neurons was 92% of the number of cresyl violet-stained neurons and the number of DiI (+) neurons 95.6% of TH-(+) neurons. Thus, the DiI (+) and TH-(+) neurons seems to represent the same neuronal population and this is close to 90% of the dopaminergic neurons in SNpc.

Degree and time course of SNpc neuronal loss after transection of MFB

The total number of DiI neurons and size of neurons after transection are listed in Table 1. The percentage of loss of SNpc neurons compared with control side at 1, 2, 4, 6, 10, 12 and 16 weeks after a unilateral mechanical lesion of the MFB were 38.7, 63.2, 71.1, 94.9, 94.3, 95, 93.9, 92.3%, consecutively. Sizes of neurons were also

Table 1. *Total number and size of labeled DiI neurons after transection*

	Control side	Lesion side	Size of neuron
Normal	4037 ± 161*		20.3 ± 5.8
1 week	3985 ± 149	2444 ± 432	18.8 ± 4.3
2 weeks	3634 ± 78	1338 ± 71	17.5 ± 4.2
3 weeks	3749 ± 106	1120 ± 106	16.1 ± 3.3
4 weeks	3635 ± 68	185 ± 47	15.3 ± 4.4
8 weeks	4218 ± 60	240 ± 10	17.1 ± 1.4
10 weeks	3761 ± 88	188 ± 19	17.3 ± 2.3
12 weeks	3664 ± 90	223 ± 15	16.1 ± 1.2
16 weeks	3655 ± 84	281 ± 18	16.3 ± 1.8

*Numbers are expressed Mean ± SEM.

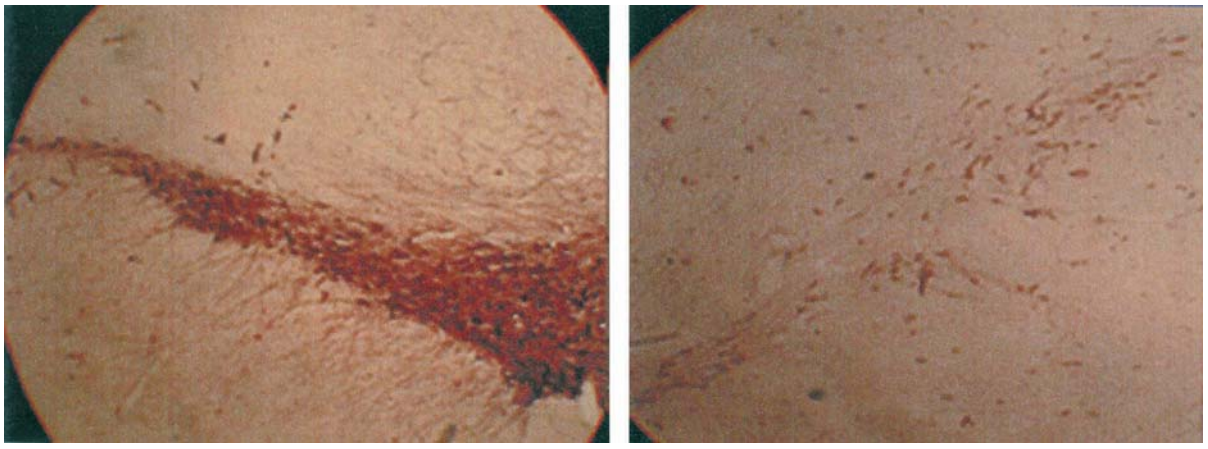

Fig. 3. Representative pictures showing axotomy-induced degeneration of SNpc neurons with time; intact side of SNpc 4-weeks post-transection showing TH-(+) neurons (*left*), transected side showing complete neuronal loss in SNpc (*right*)

decreased after transection. There was a significant drop in the number of surviving neurons after the first week, followed by a modest degree of decrement during the second to third week, but another steep decline after the third week. Beyond this time, there were no significant changes in the number of surviving neurons until 16 weeks, shown as plateau.

Approximately 40% of cells died within the first week after the lesion, followed by a progressive cell loss, with a leveling off at approximately 95% cell loss after about 4 weeks (Fig. 3). There were no significant changes with regard to number of surviving neurons. There is a clear correlation, as might be expected, between the completeness of lesion achieved and the degree of resulting cell death. Notably, even at complete transection, as judged by an almost complete absence of tracer in the ipsilateral striatum, about 5–7.7% of the nigral neurons survived. This lack of tracer in the most complete lesions, coupled with the distribution of surviving cells, suggests possible existence of contralaterally projecting SN neurons. After 4 weeks up to 16 weeks, the same relationship between completeness of lesion and degree of cell death can be seen, representing the absence of any significant regeneration of SNpc neurons after complete transection of their axons projecting to the targeted region, the striatum.

Disscussion

This study has shown that following a mechanical transection of the MFB, there is an almost complete loss of TH-neurons from the SN. This loss progresses linearly reaching an end point at about 4 weeks at which time only 5.1% of SNpc neurons remain. However, it is associated with a somewhat biphasic pattern with two sharp declines from time of transection to first week, and third week to fourth week, with modest to plateau curve in between. It may be due to an early response of SNpc neurons to complete axotomy followed by delay in neuronal loss associated with compensatory induction and upregulation, of TH expression or other mechanisms involving restorative processes of dying neurons, but then ensuing continued cell death without regenerative process. The exact mechanism of neuronal death with regard to time and degree of cell death should be verified in future with a quantitative study on up- or down-regulation of various factors involved in the degeneration and regeneration of specific axons and neurons in SN and striatum. In this study, the cell loss in SNpc was attributable to cell death and not merely a down-regulation of TH, as was demonstrated by the injection of a retrograde tracer, DiI, into the striatum seven days before the transection.

DiI labelling has been shown not to affect the survival of neurons in vitro and in vivo, and remains robustly detectable up to 9 months in vivo without leakage to other cells [15, 20]. Its retrograde transporting capability is based to a large part on passive diffusion through association with lipids, including cellular membranes, and results in the ‘‘filling’’ or labeling of neuronal cell body and all processes [4, 9]. This was also observed in this study where survived neurons, previously labeled with DiI, up to 10 weeks maintained its labeling without fading. Also, with the dose as used in this experiment, it has been shown to cover the whole striatum, thus labeling most of the axons of SNpc neurons in striatum. However, it was associated with a somewhat strong background which, due to its strong fluorescence, sometimes interfered with

the visualization of the outline of surviving neurons. Labeling with a lesser dose may in future solve this problem.

The wire knife used in this study is similar to the wire knife developed by Scouten *et al.* [27] but it is simpler, stronger, and inexpensive as well as effective in transecting most of, if not all, nigrostriatal axonal pathway as demonstrated in earlier studies. It is mainly made of platinum-tongsten steel and is custom-designed to have a memory effect so that it would be kept straight within the guide-canula, but will have a circular configuration when pushed-out from the canula. It is 100-μm thick, 3-mm wide and 3-mm high. From previous and the present study, it has been proved to be simple in use, have good endurance (each lasting more than one year), and to be much less expensive as compared to commercial products. When the purpose of research is to seek therapeutic effects of certain drugs or therapeutic modalities that require a definitive and consistent model, the authors believe that this model would be ideal because it provides a complete hemi-Parkinson model in a short period of time. However, it would not be suitable for studying similar to clinical syndromes when a slower, selective and progressive dying of SNpc neurons is preferred. This type of model, more related to human Parkinson disease, however, may also be quantified in chronological order by modifying the transection technique. This technique is currently under investigation and will be very attractive if and when it is possible to repeat with consistency any degree of transection and degree of neuronal degeneration of SNpc.

As for the number of DiI (+) and TH-(+) neurons counted in the control groups, results showed that percentage of DiI (+) neurons among TH-(+) neurons was 95.6%, meaning that retrograde DiI labeling was essentially complete. Also, results indicated that DiI (+) and TH-(+) neurons represent 88 and 92% of cresyl violet stained neurons and TH-(+) neurons represent 92% of cresyl violet stained neurons. These figures are similar to previous studies [11]. The remaining portion, about 10%, may represent the uncounted neurons due to small size (<10 μm in diameter) or non-dopaminergic neurons normally present in SNpc along with dopaminergic neurons that account for the majority of neurons in this area. Such smaller sized neurons may also be dopaminergic but were not counted because they may represent intrinsic or interneurons that exclusively reside in SNpc without their axons projecting to the striatum. Thus, the retrogradely labeled DiI (+) neurons and TH-immunoreactive neurons in this study very likely represent the same neuronal population and this is close to 90% of the dopaminergic neurons in SNpc.

Following transection of the MFB, 40, 63, 70, 95, 94, 95, 94, and 93% ipsilateral cell death in the SN was achieved within 1–4, 8, 10, 12, 16 weeks, respectively, whilst terminals in the striatum completely lose TH immunoreactivity within the first week. The data presented above suggest that pure axotomy of the nigrostriatal tract took approximately 4 weeks to cause maximum neuronal loss in the SN in our study. This number showed no significant change beyond 4 weeks (and up to 16 weeks) indicating no regeneration of nigral neurons after complete axotomy takes place. The degree and time course of cell death following axotomy in this study were more complete after much shorter time intervals compared with other studies involving mechanical injury of nigrostriatal pathway [2, 11, 16] or electrolytic lesion of the MFB where TH activity in the SN is reduced to 40% of the control level by 14 days and remains at this level until at least 60 days after the lesion [25]. This may perhaps be explained by the fact that damaging of axons closer to cell bodies was possible with the technique used here. Thus, this model provides a complete hemitransection model with a degree similar to those from neurotoxin but at the same time preserving anatomical structures in both SN, striatum, and nigrostriatal pathway rostral to the transection. It represents a simple, inexpensive, ideal model for the study of degeneration and regeneration for various purposes.

References

1. Abercrombi M (1946) Estimation of nuclear population from microtome sections. Anat Rec 94: 239–247
2. Agnati LF, Fuxe K, Calza L, Benfenati F, Cavicchioli L, Toffano G, Goldstein M (1983) Gangliosides increase the survival of lesioned nigral dopamine neurons and favour the recovery of dopaminergic synaptic function in striatum of rats by collateral sprouting. Acta physiol 119: 347–363
3. Battista A, Fuxe K, Goldstein M, Miyamoto T (1974) Effect of ventromedial tegmental lesions on central catecholamine neurons of monkey brain: involvement of dopamine pathways in tremor and involuntary movements. Med Biol 52: 66–69
4. Bentivoglio MH, Kuypers HG, Catsman-Berreveots CE, Dann O (1980) Two new fluorescent tracers which are transported over long distances. Neurosci Lett 18: 25–30
5. Beresford WA (1965) A discussion on retrograde changes in nerve fibres. Prog Brain Res 14: 33
6. Bjorklund A, Lindvall O (1984) Dopamine-containing systems in the CNS. In: Bjorklund A, Hiikfelt T (eds) Handbook of chemical neuroanatomy, vol. 2: classical transmitters in the CNS, part 1. Elsevier Amsterdam, pp 55–57
7. Bowenkamp KE, David D, Lapchak P (1996) 6-hydroxydopamine induces the loss of the dopaminergic phenotype in substantia nigra neurons of the rat. A possible mechanism for restoration of the

nigrostriatal circuit mediated by glial cell line-derived neurotrophic factor. Expl Brain Res 111: 1–7
8. Clatterbuck RE, Price DL, Koliatsos VE (1993) Ciliary neurotrophic factor prevents retrograde neuronal death in the adult central nervous system. Proc Nat Acad Sci 90: 2222–2226
9. Divac I, Mogensen J (1990) Long term retrograde labelling of neurons. Brain Res 524: 339–341
10. Ehringer H, Hornykiewicz O (1960) Verteilung von Noradrenalin und Dopamin (3-Hydroxytyramin) im Gehirn des Menschen und ihr Verhalten bei Erkrankungen des extrapyramidalen Systems. Klin Wschr 38: 1236–1239
11. Hagg T, Varon S (1993) Ciliary neurotrophic factor prevents degeneration of adult rat substantia nigra dopaminergic neurons in vivo. Proc Natl Acad Sci USA 90(13): 6315–6319
12. Hassler R (1955) The pathological and pathophysiological basis of tremor and parkinsonism. Proc 2nd Int Congr Neuropath Lond 1: 29–58
13. Hekkita RE, Hess A, Duvoisin RC (1984) Dopaminergic neurotoxicity of 1-methyl-4-phenyl-1,2,5,6-tetrahdropyridine in mice. Science 224: 1451–1453
14. Hokfelt T, Ungerstedt U (1974) The degeneration pattern of the nigro-neostriatal dopamine system after electrothermic or 6-hydroxy-dopamine lesions. In: Fuxe K, Olson L, Zotterman Y (eds) Dynamics of degeneration and growth in neurons. Pergamon Oxford, pp 19–28
15. Honig MG, Hune RI (1986) Fluorescent carbocyanine dyes allow living neurons of identified origin to be studied in long-term cultures. J Cell Biol 103: 171–187
16. Janson AM, Fuxe K, Agnati LF, Kitayman I, Harfstrand A, Andersson K, Goldstein M (1988) Chronic nicotine treatment counteracts the disappearance of tyrosine-hydroxylase-immunoreactive nerve cell bodies, dendrites and terminals in the mesostriatal dopamine system of the male rat after partial hemitransection. Brain Res 455: 332–345
17. Knusel B, Beck KD, Winslow JW, Rosenthal A, Burton LE, Widmer HR, Nikolics K, Hefti F (1992) Brain-derived neurotrophic factor administration protects basal forebrain cholinergic but not nigral dopaminergic neurons from degenerative changes after axotomy in the adult rat brain. J Neurosci 12: 4391–4402
18. Lapchak PA, Beck KD, Araujo DM, Irwin I, Langston JW, Hefti F (1993) Chronic intranigral administration of brain-derived neurotrophic factor produces striatal dopaminergic hypofunction in unlesioned adult rats and fails to attenuate the decline of striatal dopaminergic function following medial forebrain bundle transection. Neuroscience 53: 639–650
19. Loughlin SE, Fallon JH (1982) Mesostriatal projections from ventral tegmentum and dorsal raphe: cells project ipsilaterally or contralaterally but not bilaterally. Neurosci Lett 32: 1l–16
20. Manuel VS, Maria PVP, Bray GM, Aguayo J (1988) Persistent retrograde labeling of adult rat retinal ganglion cells with the carbocyanine dye DiI. Exp Neurol 102: 92–101
21. Moore RY (1978) Surgical and chemical lesion techniques. In: Iversen LL, Iversen SD, Snyder SH (eds) Handbook of psychopharmacology, vol. 9. Plenum Press, New York, pp l–39
22. Paxinos G, Watson C (1986) The rat brain in stereotaxic coordinates, 2nd edn. Academic Press, Sydney
23. Perese DA, Ulman J, Viola J (1989) A 6-hydroxydopamine induced selective parkinsonian rat model. Brain Res 494: 285–293
24. Perry VH, Gordon S (1991) Macrophages and the nervous system. Int Rea Cytol 125: 203–244
25. Reis DJ, Gilad G, Pickel VM, Joh TH (1978) Reversible changes in the activities and amounts of tyrosine hydroxylase in dopamine neurons of the substantia nigra in response to axonal injury as studied by immunochemical and immunocytochemical methods. Brain Res 144: 325–342
26. Sakai K, Gash DM (1994) Effect of bilateral 6-OHDA lesions of the substantia nigra on locomotor activity in the rat. Brain Res 633: 144–150
27. Scouten CW, Cegavske CF, Rozboril L (1980) A versatile carrier for simply constructed wire knives and microsyringes. Physiol Beh 26: 1115–l119
28. Sofroniew MV, Galletly NP, Isacson O, Svendsen CN (1990) Survival of adult basal forebrain cholinergic neurons after loss of target neurons. Science 247: 338–341
29. Sotelo C, Javoy F, Agid Y, Glowinski J (1973) Injection of 6-hydroxydopamine in the substantia nigra of the rat. I. Morphological study. Brain Res 58: 269–290
30. Ueki A, Rosen L, Andbier B, Finnaman U, Altamimi U, Janson AM, Goldstein M, Aanati LF, Fuxe K (1993) The vigilance-promoting drug modafinil counteracts the reduction of tyrosine-hydroxylase immunoreactivity and of dopamine stores in nigrostriatal dopamine neurons in the male rat after a partial transection of the dopamine pathway. Expl Brain Res 93: 259–270
31. Ungerstedt U (1968) 6-Hydroxydopamine induced degeneration of central monoamine neurons. Eur J Pharmac 5: 107–110

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