T. Kanno (Editor in Chief)
Y. Kato (Ed.)

Minimally Invasive Neurosurgery and Multidisciplinary Neurotraumatology

Springer

T. Kanno (Editor in Chief)
Y. Kato (Ed.)

Minimally Invasive Neurosurgery and Multidisciplinary Neurotraumatology

With 158 Figures, Including 14 in Color

Springer

Tetsuo Kanno, M.D., Ph.D.
Professor, Department of Neurosurgery, School of Medicine, Fujita Health University 1-98 Dengakugakubo, Kutsukake-cho, Toyoake, Aichi 470-1192, Japan

Yoko Kato, M.D., Ph.D.
Associate Professor, Department of Neurosurgery, School of Medicine, Fujita Health University 1-98 Dengakugakubo, Kutsukake-cho, Toyoake, Aichi 470-1192, Japan

Library of Congress Control Number: 2005936510

ISBN-10 4-431-28551-2 Springer-Verlag Tokyo Berlin Heidelberg New York
ISBN-13 978-4-431-28551-9 Springer-Verlag Tokyo Berlin Heidelberg New York

Springer is a part of Springer Science+Business Media
springeronline.com

Printed in Japan

Typesetting: SNP Best-set Typesetter Ltd., Hong Kong
Printing and binding: Shinano Inc., Japan

Printed on acid-free paper

Preface

Two meetings took place simultaneously in Nagoya in March 2005. Both the 6th International Congress of Minimally Invasive Neurosurgery (MIN) and the 3rd World Congress of the Academy for Multidisciplinary Neurotraumatology (AMN) were held at the same venue and successfully brought together experts in different areas of clinical neuroscience and neurosurgical subspecialties. With apparently quite different problems to deal with, both congresses had a lot in common. They brought specialists working in different areas closer together with the goals of applying the latest front-line instrumentation to the improvement of neurosurgical operative technique through less invasiveness and finding the optimal multidisciplinary approach for patients with neurotrauma, for whom neurosurgery alone is insufficient to ensure full recovery.

The ultimate goal of neurosurgeons is to minimize injury to the nervous system through their interventions and to create the best conditions for recovery. The concept of minimal invasiveness has evolved throughout the history of neurosurgery, blossoming in the last two decades as a result of technological improvements in neurosurgical instrumentation. These advances have been applied across all neurosurgical subspecialties and are not specific to any type of pathology or anatomical area. This has produced a revolutionary shift in neurosurgical practice in the operating room. However, minimal invasiveness does not directly translate as "neurosurgery of minimal surgical trauma." The design of minimally invasive instrumentation has rapidly produced many new types of tools, requiring new basic and clinical knowledge combined at times with totally different surgical skills. Only after achieving these skills can neurosurgeons embark on the application of these new surgical procedures. This combination of scientific information and know-how, as in the whole science and art of neurosurgery, has to be obtained with the guidance of a mentor. Only in the hands of the knowledgeable, skilled, and experienced can the goal of minimal trauma through minimal invasiveness be achieved.

The trend toward minimal invasiveness will continue to progress and result in the ongoing refinement of neurosurgery. Minimally invasive techniques have already become part of the basic training of neurosurgical specialists. The spread of this idea and its realization out of a few specialized centers, convincing disbelieving traditionalists and realistically instructing the willing to improve their neurosurgical technique, have been the objectives of this meeting.

Neurotraumatology patients present an enormous challenge to society. Neurosurgical management of brain and spinal cord injury has been a frustrating area, as surgical methods, especially in moderate and severe injuries, have been limited to control of brain and spinal compression, control of intracranial pressure with its expected effect on cerebral blood flow, and structural repair of the supporting structures (skull, spine, brain and spinal cord coverings). Achieving the best outcome for the neurotraumatology patient, however, requires much more than that. This important issue has thus far been approached through the broadest spectrum of scientific knowledge, from the most fundamental biological sciences to the social sciences. Such a variety of approaches has for a long time been in need of a "center of gravity," a balancing point where facts and opinions can meet and be integrated. The management of neural injury is awaiting a breakthrough, and we should do our best to facilitate. As the majority of the new discoveries tend to appear at the integrating borderlines of two separate scientific areas, our duty is to bring together all scientists involved with neural injury. We all hope that the meeting has fulfilled this goal and is a step forward in bringing together previously distant areas of knowledge in neurotraumatology.

These proceedings contain the full text of the submitted reports, with the intention of providing the information and personal opinions of the participating speakers to those who were unable to attend. Although the discussions (sometimes containing the great wisdom of common sense and impressions from practice) are not included, we believe that readers will be able to obtain an accurate picture of events and their content. We hope that this book will attract them to these fascinating areas of innovation in clinical neuroscience.

Tetsuo Kanno
President of the 6th MIN and the 3rd AMN
Aichi, Japan

Contents

List of Contributors

Part 1
6th International Congress on Minimally Invasive Neurosurgery

The NASA Smart Probe for Real-time Tissue Identification: Potential Applications in Neurosurgery

Russell Andrews[1], Robert Mah[1], Richard Papasin[1], Michael Guerrero[1], and Luis DaSilva[2]

Summary. Minimally-invasive neurosurgery depends on accurate identification of tissues, frequently under conditions of impaired visualization (e.g. endoscopic images). The NASA Smart Probe employs neural networks to integrate data from multiple microsensors in real-time to create a unique tissue "signature" for each tissue. The Smart Probe concept is reviewed and clinical data from women with suspected breast cancer (by the NASA licensee, BioLuminate Inc.) are summarized. The breast cancer Smart Probe utilizes electrical impedance and optical spectroscopy (both broadband or white light, and laser light (infrared and blue/fluorescence)) microsensors in a 1 mm diameter probe. Data are acquired 100 times per second, with a typical 15 s a breast "biopsy" typically generating several hundred megabytes (MB) of data. The multiparameter "Smart Probe" can readily differentiate both normal tissues and carcinoma.

Key words. microsensors, neural networks, optical biopsy, robotics, spectroscopy

1 Introduction

It has been well-documented over the last 10 years that optical spectroscopy can identify tissue in real time, e.g. normal versus cancerous tissue in the breast, and white versus gray matter in the brain [1–3]. A light scattering spectroscopy probe has been shown to be at least as accurate as—if not more accurate than—a well-trained pathologist's review of tissue specimens [4]. However, both the operating room and outer space represent "hostile" environments where the redundancy of multiple sensors is essential for reliable tissue identification. The NASA Smart Probe Project utilizes neural network and fuzzy logic algorithms to integrate data from multiple microsensors in real time for tissue identification (Fig 1). We here review the Smart Probe concept developed at NASA Ames Research Center as well as data from 23 women undergoing biopsy for suspected breast cancer using the multiparameter probe devel-

[1] NASA Ames Smart Systems, Moffett Field, 244 Mistletoe Road, Los Gatos, CA 95032, and [2] BioLuminate, Dublin, CA, USA

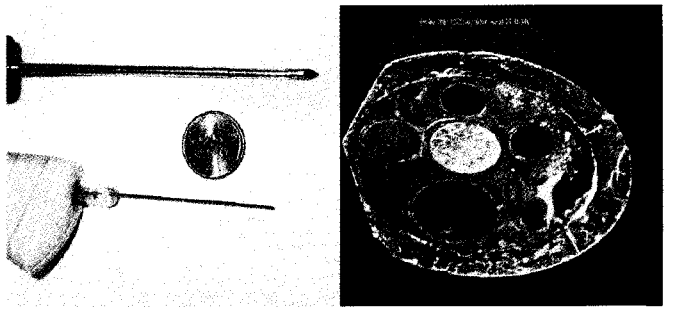


FIG. 2. BioLuminate Breast Biopsy Probe. Left: Standard Breast Biopsy Needle. Right: Beveled Tip of Probe (<1 mm Diameter)

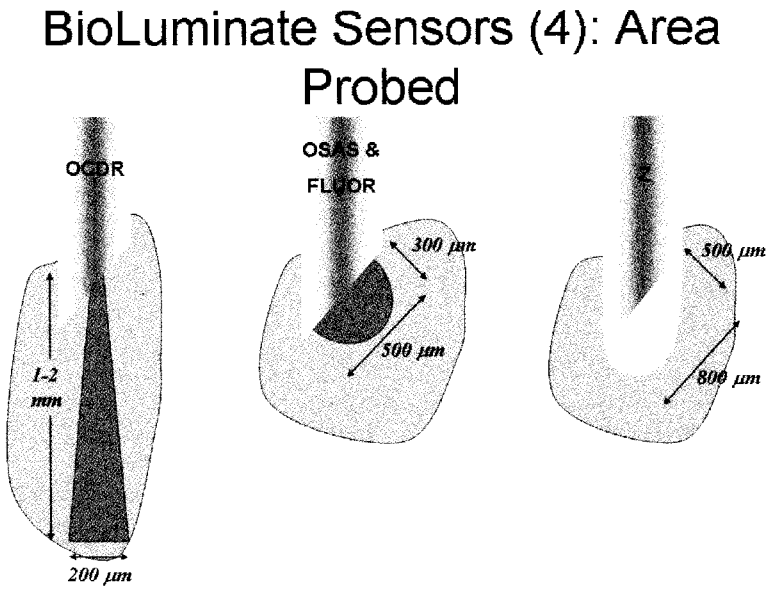


FIG. 3. BioLuminate Probe Sensors. Left to right: infrared laser spectroscopy sensor, white light (broadband) and blue laser spectroscopy sensors, and electrical impedance sensor. Typical cell size 10–40 μm, therefore; OCDR ~ 1,200–80,000 cells; OSAS & fluor & Z ~ 500–45,000 cells

University or California, San Francisco, Medical Centers. In every patient, the data acquired by the BP were diagnostic (i.e. concurred with histopathological diagnosis). Consistent with previous findings in the literature [2,3], the white (broadband) spectroscopy data contrasting the tumor oxyhemoglobin at the edge versus at the center found the oxyhemoglobin fraction at the center typically to be less than 50% that at the edge. Also consistent with the literature on electrical impedance in breast tissues [2], the electrical impedance progressively decreased from normal breast to edge of carcinoma to center of carcinoma over the frequency range 2–2,000 kHz, the greatest

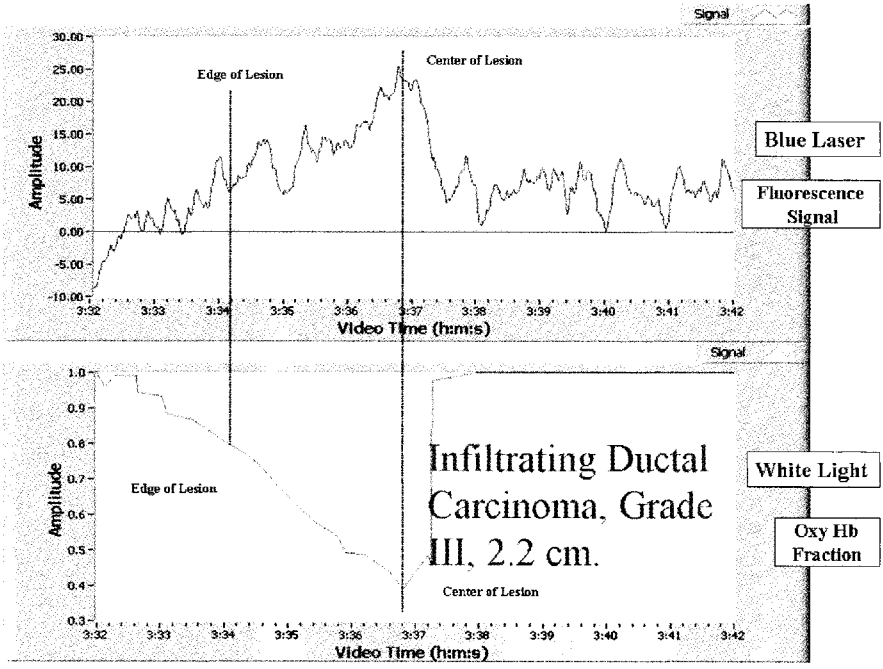


FIG. 4. Patient with infiltrating ductal breast carcinoma, grade III. Top: blue laser (fluorescence). Bottom: white/broadband (oxy Hb fraction)

difference being at the lowest frequency (2 kHz). At 2 kHz the impedance approximately doubled from the center of the breast carcinoma (~20 kOhm) to the edge of the breast carcinoma (~38 kOhm) and doubled again from the edge of the breast carcinoma to the normal breast tissue (~75 kOhm). As an illustration, Fig. 4 presents probe track data for both blue laser (fluorescence) and white (broadband, oxyhemoglobin fraction) spectroscopy contrasting the edge and the center of the carcinoma: the amplitude increased in the center in the fluorescence spectroscopy, and decreased in the broadband (white light) spectroscopy, versus the edge of the carcinoma.

4 Conclusions

The NASA Smart Probe not only incorporates data from multiple microsensors, but also incorporates many varieties of patient data (imaging, laboratory, demographic)—using fuzzy logic and neural networks to create a unique "signature" for each tissue type (e.g. benign versus malignant breast tumor versus normal breast). The BioLuminate Probe shows that a clinically-efficient device, using these techniques, can gather large amounts of data and distinguish in virtually real-time breast tissue versus benign breast masses versus breast carcinoma in the real-world setting of breast biopsy in humans. Potential applications of the Smart Probe include: (1) distinguishing tissue types (disk versus nerve root during endoscopic spine surgery), (2)

monitoring tissue in ischemia (stroke, head injury), (3) locating and/or monitoring specific regions of the brain for deep brain stimulation (movement disorders, epilepsy) and (4) the sensor for a self-contained surgical robot that may accompany future Space missions [6].

References

1. Mourant JR, Bigio IJ, Boyer J, et al (1996) Elastic scattering spectroscopy as a diagnostic tool for differentiating pathologies in the gastrointestinal tract. J Biomed Opt 1:192–199
2. Alfano RR (ed.) (1998) Advances in optical biopsy and optical mammography, vol. 838. Ann N Y Acad Sci, NY
3. Bigio IJ, Bown SG, Briggs G, et al (2000) Diagnosis of breast cancer using elastic-scattering spectroscopy: preliminary clinical results. J Biomed Opt 5:221–228
4. Wallace MB, Perelman LT, Backman V, et al (2000) Endoscopic detection of dysplasia in patients with Barrett's esophagus using light-scattering spectroscopy. Gastroenterology 119:677–682
5. Andrews R, Mah R (2003) The NASA Smart Probe project for real-time multiple microsensor tissue recognition. Stereotact Funct Neurosurg 80:114–119
6. Andrews R, Mah R, Jeffrey S, et al (2003) The NASA Smart Probe project for real-time multiple microsensor tissue recognition: Update. Proceedings of the 17th International Computer Assisted Radiology and Surgery Congress—International Congress Series 1256:547–554

Clinically Non-functional Pituitary Tumors: The Surgical and Biological Challenge

CHHENG-ORN EVANS[1], RAGUVEER K. HALKAR[2], and NELSON M. OYESIKU[1]

Summary. Non-functioning (NF) pituitary adenomas account for approximately 30% of pituitary tumors [1], reflecting the fact that these tumors do not cause clinical hormone hypersecretion [2]. They typically are quite large, and cause hypopituitarism or visual loss from regional compression. There is no available effective medical therapy for the NF tumors. We have identified new molecular targets and have developed a novel molecular-targeted imaging agent to non-functional pituitary adenomas [3].

Tumor specimens from surgery were used in these studies. Microarray analyses, RT-qPCR, Western blotting, immunochemistry and folate-binding studies were performed to determine folate receptor (FR) expression. Primary cell culture, folate-PEG-Liposome uptake, folate-PEG-Liposome-DOX uptake and cytotoxicity studies were performed. In vivo imaging was performed by injection of Folatescan and planar—SPECT/CT imaging. The FR was significantly and uniquely upregulated in non-functional pituitary adenomas [4]. Folate-PEG-liposomes with doxorubicin induced cell-death in FRα expressing pituitary tumors in vitro. Folatescan (FR targeted technetium-99) imaged FR expressing tumors. Non-FR expressing tumors were not imaged. Imaging was validated by Westerns blotting analysis.

Key words. pituitary adenoma, molecular targeting, molecular imaging, folate receptor, Folatescan

Departments of [1] Neurosurgery and [2] Radiology, Emory University School of Medicine, 1365-B Clifton Rd, NE, Ste. 6400, Atlanta, GA 30322, U.S.A.

1 Introduction

Clinically non-functional (NF) tumors cause hypopituitarism or blindness and there is no available medical treatment or specific imaging technique for these tumors. The term non-functioning reflects the fact that these tumors do not cause clinical hormone hypersecretion [2]. We discovered that FRα mRNA is uniquely overexpressed in NF tumors, and the FRα holds significant promise for medical treatment for NF tumors by enabling molecular imaging and targeting of NF tumors to identify and select tumors that may respond to folate targeted therapy. We demonstrate that FRα receptor targeting with folate coupled cytotoxic agents can inhibit tumor proliferation and that an FRα targeted imaging agent can identify FRα—expressing pituitary tumors by radionuclide imaging in vivo[3,4].

1.1 Diagnosis

MRI defines the exact anatomical configuration of the adenoma [5,6] and is essential for surgical planning. Visual examinations are necessary preoperatively and postoperatively to document visual deficit and monitor changes. Endocrine function testing is needed to determine loss of hormonal function–basal levels by themselves may not reveal hypofunction.

1.2 Treatment

The usual treatment of a non-functioning pituitary adenoma in a medically stable patient is transsphenoidal removal of the tumor [2,7,8]. If vision loss is rapid or the adenoma is associated with hemorrhage or infraction, a more urgent surgical approach is needed [9].

Radiation therapy can be used in patients with non-functioning pituitary adenomas in patients who have a significant amount of residual tumor or recurrence [10]. If the patient is elderly or medically unstable, radiation therapy may be the only viable treatment. Stereotactic radiosurgery is preferable to conventional external when the tumor configuration relative to the chiasm and optic nerves is favorable.

Radiation therapy controls tumor growth in 80–98% of patients with non-functioning tumors [10]. Hypopituitarism is the most common side effect of pituitary irradiation with an incidence of 13–56%. Long-term overall risk for brain necrosis is estimated at 0.2%. Other side effects are rare, they include optic neuropathy in 1.7%, vascular changes in 6.3%, neuropsychological problems in 0.7% and secondary malignancies in 0.8% [11]. Despite the frequent dural invasion of these tumors, many patients do well for long periods of time without radiation therapy.

1.3 Surgical Outcome

Following operative decompression of non-functioning adenomas, vision improves in approximately 80% of patients. Generally, endocrine function is the same pre- and postoperatively, although transsphenoidal surgery usually stops progressive loss of hormonal function. Unfortunately, approximately one third of patients with non-functioning adenomas have some hypopituitaryism before their surgical treatment

[12]. Postoperative evaluation with MRI and CT is best delayed for two to three months post-surgery because of postoperative changes.

1.4 Follow Up

Most patients with non-functioning pituitary adenomas should have annual MRI or CT, visual and endocrine evaluations whether or not they have had surgical or radiation treatment. If these tumors are not treated, they grow slowly over months or years. There is a significant recurrence rate following transsphenoidal surgery (approximately 10–20%). A significant number of patients who undergo postoperative radiation therapy develop hypopituitaryism and should be monitored.

2 Molecular Targeting

2.1 Folate-PEG-Liposomes Uptake in Primary Culture of Human Pituitary Adenoma Cells

Briefly, human pituitary tumor cells, NF and PRL, (50,000 cells) were plated in folate free RPMI and 10% fetal bovine serum (v/v) for 3 days at 37°C, 5% CO_2. Folate-PEG-liposomes encapsulating calcein (10 mM internal concentration) were diluted in 1 ml of folate free RPMI, added to the cells and incubated at 37°C for 2 h. To demonstrate competitive uptake and specificity for folate, 10 µl of folic acid (100 mM) was added to another 1 ml of folate free culture for 15 min prior to adding the liposomes. The culture was incubated at 37°C for 2 h. Cells were washed twice with PBS, cytospun into the Superfrost/Plus microscope slides (Fisherbrand, Fisher Scientific, Pittsburgh, PA). After washing with PBS, the nuclei were stained by DAPI for 10 min. Cover slips were mounted on Prolong Anti-Fade mounting medium (Biomeda corp. Foster City, CA), imaged with a BX40 or a BX60 microscope (Nikon ECLIPSE TE300, Nikon Instruments Inc., Melville, NY), and photographed (Fig. 1a–c).

2.2 Western Blotting Analysis

Total protein (10 µg or 20 µg) of each sample was separated by a 15% SDS-PAGE. Immunodetection was carried out using a polyclonal antibody, rabbit anti-human FR IgG (Figs 2c and 3).

2.3 Folate-PEG-Liposome-DOX Uptake by Primary Culture of Human NF Pituitary Adenomas

Human NF pituitary adenoma cells were plated (5×10^4 cells per well) in 1 ml folate free RPMI and 10% fetal bovine serum for 72 h at 37°C, 5% CO_2. Targeted Folate-PEG-liposome DOX (Doxorubicin) or non-targeted liposomes (PEG-Liposomes-DOX) (50 ug/ml) was added to each well. Cells were incubated for 2 h with the DOX mixture at 37°C in a 5% CO_2. After washing 3 times with 1 ml of ice cold PBS with Ca and Mg to remove extracellular DOX, cells were lysed with 500 µl of 5% Triton X-100. The flu-

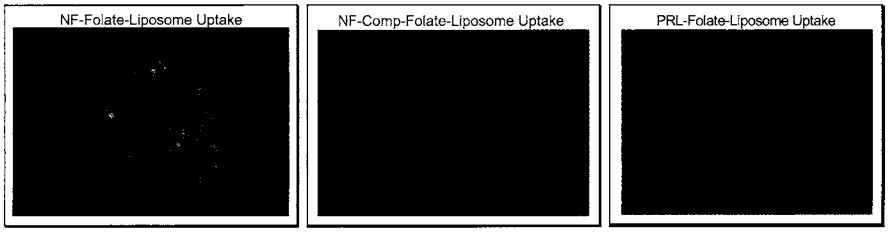


FIG. 1. **a** Folate-PEG-Liposome Uptake in Primary culture of Human NF Pituitary Adenoma Cells (magnification ×600): fluorescence micrograph demonstrates uptake of calcein-loaded folate-PEG liposomes into FRα- expressing human pituitary adenoma cells. Note that calcein fulorescence is seen in the small round adenoma cells double-labeled with DAPI. **b** Competition of Folate-PEG-Liposomes with Folic acid in Human NF Pituitary Adenoma Cells (magnification ×60): fluorescence micrograph demonstrates *inhibition* of uptake of calcein-loaded folate-PEG liposomes into FRα- receptor positive human pituitary adenoma cells in the presence of free folate. Cell nuclei are labeled with DAPI. **c** Folate-PEG-Liposome Uptake in Primary culture of Human PRL Pituitary Adenoma Cells (magnification ×400): fluorescence micrograph demonstrates no uptake of calcein-loaded folate-PEG liposomes into FRα- receptor negative human pituitary PRL adenoma cells. Cell nuclei are loaded with DAPI

orescence intensity of the lysed cell solution was measured on a fluorescence Spectrometer (Perkin-Elmer, Shelton, CT) at 475/580 nm. A standard curve of DOX uptake was performed (Fig. 2**a**).

2.4 MTT Cytotoxicity Assay of DOX in Primary Culture of Human NF Pituitary Adenomas

Human NF pituitary adenoma cells were transferred to a 96-well plate at a density of 5×10^3 cells per well 24 h prior to the assay. The culture medium (folate free RPMI) was replaced with 100 µl of medium with serial dilutions of Folate-PEG-liposome-DOX and folate free (RPMI) as control (Fig. 2**b**). To confirm specificity for folate-mediated uptake of liposome, a free ligand competition experiment using excess folic acid was performed by adding 1 mM folic acid to the medium prior to adding the folate-PEG-liposome-DOX. After 2 h incubation at 37°C, the cells were washed 4 times with PBS and incubated in fresh culture medium for a further 48 h. Next, the media was removed and 100 µl of fresh media was added. Then 25 µl of 5 mg/ml MTT dissolved in PBS was added to each well and cells were incubated for 2 h at 37°C. The medium was removed and the cells were solubilized in 100 µl of DMSO. The aborbances at 570 nm and 630 nm were read. Absorbance 630 nm was used as reference (Fig. 2**b**).

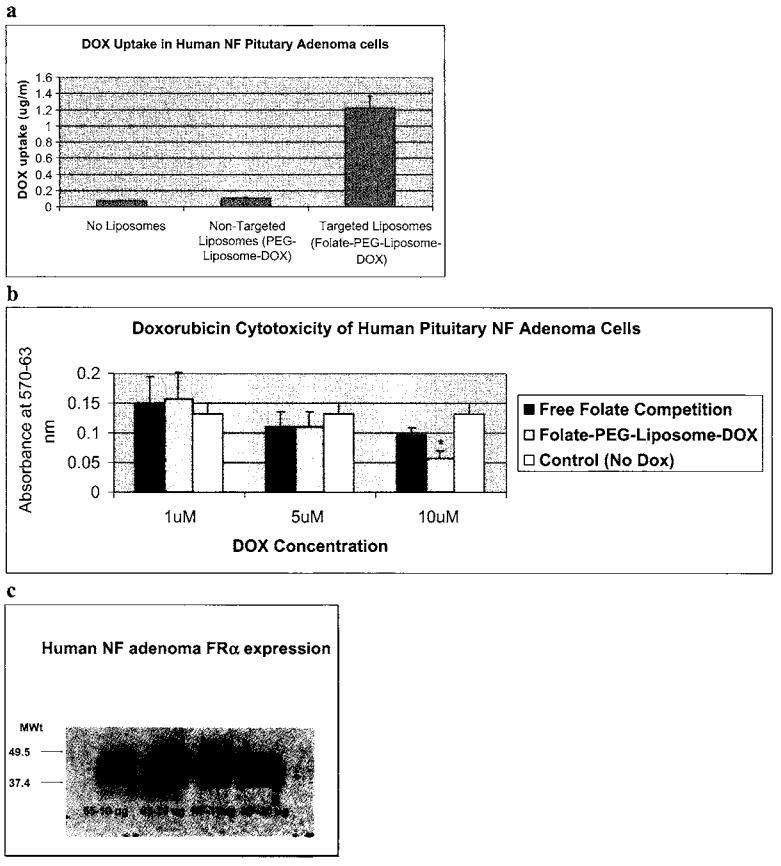


FIG. 2. **a** DOX uptake into primary human FRα expressing from targeted and non-targeted liposomes in culture. DOX targeted liposomes are significantly taken up compared with non-targeted liposomes into the FRα human adenoma cells ($n = 3$). (t-test shows a significant difference between control and DOX uptake at $P < 0.01$). **b** Dose-response chart of Doxorubicin cytoxicity in FRα expressing human pituitary NF adenoma cells in cell culture. *Y-axis*: The number of viable cells in each well was determined by absorbance at 570 nm–630 nm measured on an automated plate reader. The *lower* the *absorbance*, the *greater* the *cytotoxic* effect. *X-axis*: DOX concentration. Control medium = No DOX, medium only. There was a statistically significant change in absorbance (>50%, ANOVA, $P < 0.05$) at 10 μm (*) compared with control. Data represent mean of triplicate sets. **c** Western analysis of FRα expression of human NF pituitary adenoma cells used in DOX uptake experiments Fig. 2**a** and cytotoxicity experiments in Fig. 2**b**. Lanes 1 and 2 represented positive control (10 and 20 μg of protein from tumor sample known to express FRα #65). Lanes 3 and 4 represented 10 and 20 μg of protein from tumor sample used in targeted (folate-PEG-liposome-DOX) uptake experiment Fig. 2**a** and cytotoxicity experiments in Fig. 2**a**

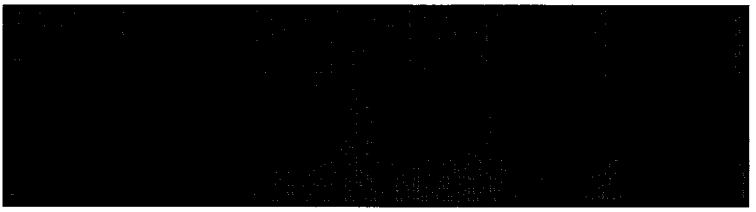


FIG. 3. FRα expression by Western analysis of human pituitary tumor samples used in Folate Scan (Figs 4 and 5). Lane 1: pituitary cell line transfected with FRα cDNA (positive control). Lane 2: human clinically NF pituitary tumor known to be FRα receptor positive (positive control) derived from PIs tumor bank (ID #65). Lanes 3 (10 μg) and 4 (20 μg) of protein from pituitary tumor sample (NF 17) from patient imaged by SPECT in Fig. 5. Tumor is FRα receptor negative. Lanes 5 (10 μg) and 6 (20 μg) of protein from pituitary tumor sample (NF18) form patient imaged by SPECT in Fig. 4. Tumor is FRα receptor positive

3 Molecular Imaging

3.1 FolateScan (Technetium Tc-99m EC20)—Single Photon Emission Computed Tomography (SPECT)/CT Imaging of Pituitary Adenomas

Each patient had a medical examination, baseline vital signs, blood and urine samples 2 h before injection. Patients received two IV injections 1–3 min apart: 1 mg of folic acid and 1–2 ml injection of 0.1 mg/666 MBq of Folatescan. The patients had mid-thigh to head planar images at 1–2 h post-injection followed by imaging using a SPECT scanner with integrated CT (GE VG/Hawkeye). SPECT images were obtained after the planar imaging. Following surgery, Western analysis was performed to detect FR expression in tumor samples [3].

4 Results and Discussion

We demonstrate that the liposomes targeted to the FRα are *selective* and *specific* for human pituitary *tumor cells in vitro*. The liposomes are endocytosed by the FRα into cultured human pituitary tumor cells that express the FRα (Fig. 1**a**) and are not taken up by human pituitary tumor cells (PRL tumor) that do not express the folate receptor α (Fig. 1**c**). The folate-targeted liposomes are competitively blocked by folic acid (Fig. 1**b**).

We demonstrate cytotoxicity of adenoma cells after uptake of folate-PEG-liposome-DOX using an MTT cytotoxicity assay. The number of viable cells in each well was determined by absorbance at 570 nm measured on an automated plate reader. The lower the absorbance, the greater the cytotoxic effect. Fig. 2**a,b** demonstrate uptake

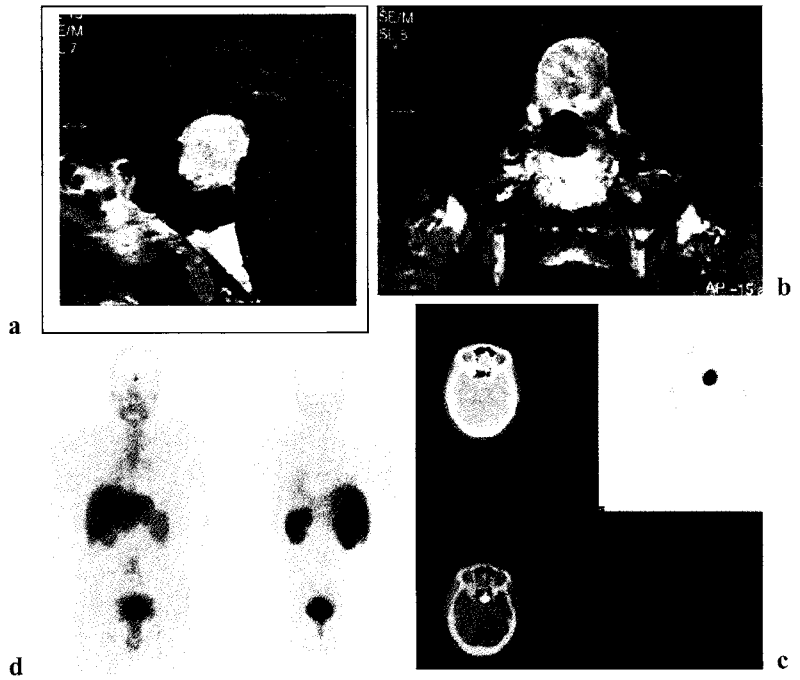


FIG. 4. MRI Images of Clinically Non-functional Pituitary Adenoma. Images are contrast-enhanced images with Gadolinium (tumor appears white against grey back ground of brain). **a** Sagittal image, **b** Coronal image. The same tumor is demonstrated in Figs 4c,d using folate receptor targeted Technetium 99 (FolateScan). **c** SPECT images with CT scan confirm the uptake within the tumor in the pituitary fossa. **d** Anterior and posterior whole body planar images showing focal intense radiotracer concentration in the folate-receptor positive pituitary tumor. Tracer distribution was found in the major routes of elimination: kidney, liver, gall bladder and urinary bladder

and cytotoxic effect of these DOX loaded liposomes. In contrast, non-targeted liposomes were not taken up by the human NF pituitary adenoma cells. Futhermore, the effect folate PEG-liposome-DOX on cytotoxicity was blocked by excess free folate competition of FRα demonstrating selectivity of the liposomes for the FRα receptor.

Student t-test shows a significant difference between control and DOX uptake at $P < 0.001$. There was a statistical difference ($P < 0.05$, *) in absorbance between folate PEG-lipoposme-DOX (10 μm) and controls (No DOX).

We also show that Folatescan SPECT/CT can detect FR+ pituitary tumors. We demonstrate the safety and efficacy of a folate-targeted imaging agent Folatescan (Technetium Tc-99m EC20; Endocyte, Inc.) consisting of technetium-99m conjugated to a folate receptor (FR) ligand (EC20) in clinically non-functional pituitary tumors. Since the FR is overexpressed in clinically non-functional tumors, uptake of Folatescan in the tumor should serve as a marker for selection of folate receptor-positive (FR+) tumors for folate-targeted therapy [3].

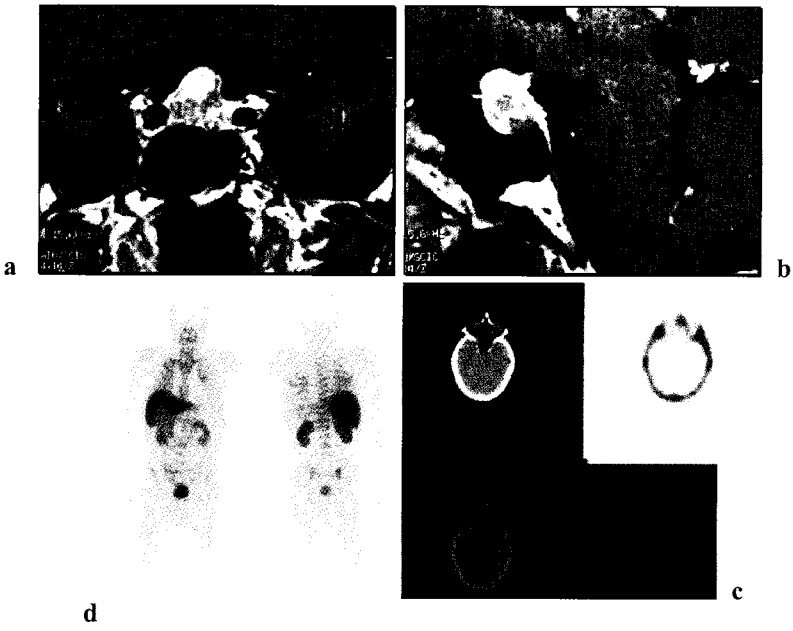


FIG. 5. MRI Images of Pituitary Adenoma. Images are contrast-enhanced images with Gadolinium (tumor appears white against grey back ground of brain). **a** is coronal images, **b** is sagittal image. The same tumor is not visualized in Fig. 5**c,d** using folate receptor targeted Technetium 99 (FolateScan). **c** (below, right panel): SPECT with CT images showed no significant uptake in the FR receptor-negative pituitary tumor. **d** (bottom, left panel): Whole body images of Tc-99m Folate showing hepatic and renal elimination, with no uptake in the folate-receptor negative pituitary tumor

Two patients were imaged prior to transsphenoidal surgery, and their planar and SPECT images were compared to Western blotting analysis. Both patients had presented with visual deficit and a hormonal profile consistent with clinically non-functioning pituitary tumor. In one patient, Folatescan successfully targeted the FR+ pituitary tumor (Fig. 4**c,d**). The Western blotting analysis validated that this tumor was FR+ positive (Fig. 3, lanes 5 and 6). In the second patient, the tumor was folate receptor negative (FR-) by Folatescan scintigraphy (Fig 5**c,d**) and was validated by lack of FR expression by Western analysis (Fig. 3, lanes 3 and 4). CT images produced by the integrated scanner were valuable in verifying the location of uptake (or the lack of uptake) in the pituitary area.

5 Conclusion

These preliminary data demonstrate that we can successfully target an imaging agent to the FR in pituitary tumors. It provides support for experiments to develop this as a novel diagnostic imaging tool for clinically non-functional tumors, which currently does not exist. Secondly, it provides preliminary evidence that a folate-tagged ligand

can potentially be used for tumor-targeted therapy by *binding to the FR* in tumors that express the receptor.

References

1. Asa SL, Kovacs K (1992) Clinically non-functioning human pituitary adenomas. Can J Neurol Sci 19:228–235
2. Katznelson L, Alexander JM, Klibanski A (1993) *Clinically nonfunctioning pituitary adenomas.* J Clin Endocrinol Metab 76:1089–1094
3. Oyesiku NM, et al (2004) *SPECT/CT of FolateScan (Tc-99m EC20) in pituitary tumors: A novel imaging tracer and Technique.* J Nucl Med 45 (5 S):368
4. Evans C-O, et al (2003) *Differential Expression of Folate Receptor in Pituitary Adenomas.* Can Research 63:4218–4224
5. Dolinskas C, Simeone F (1985) *Transsphenoidal hypophysectomy: Postsurgical CT findings.* Am J Neuroradiol 6:45–50
6. Mikhael M, Ciric I (1988) *MR imaging of pituitary tumors before and after surgical and/or medical treatment.* J Comput Assist Tomogr 12:441–445
7. Ebersold MJ, et al (1986) *Long-term results in transsphenoidal removal of nonfunctioning pituitary adenomas.* J Neurosurg 64:713–719
8. Greenman Y, Melmed S (1996) *Diagnosis and management of nonfunctioning pituitary tumors.* Annu Rev Med 47:95–106
9. Biousse V, Newman NJ, Oyesiku NM (2001) *Precipitating factors in pituitary apoplexy.* J Neurol Neurosurg Psychiatr 71:542–545
10. Milker-Zabel S, et al (2001) *Fractionated stereotactically guided radiotherapy and radiosurgery in the treatment of functional and nonfunctional adenomas of the pituitary gland.* Int J Radiat Oncol Biol Phys 50:1279–1286
11. Becker G, et al (2002) *Radiation therapy in the multimodal treatment approach of pituitary adenoma.* Strahlenther Onkol 178:173–186
12. Flickinger JC, et al (1989) *Radiotherapy of nonfunctional adenomas of the pituitary gland. Results with long-term follow-up.* Cancer 63:2409–2414

Tips for Correct Use of Navigation

Eiji Kohmura

Summary. Development of neuronavigation systems has made great contribution in the field of minimally invasive neurosurgery. Neuronavigation can help surgeons enormously so far as the information is correct. Brain shift always takes place during surgery and is a main reason of inaccuracy. We developed a gluing technique to minimize brain shift during surgery. We can glue the brain surface to the dura at the initial stage so that we create similar situation as recurrent cases where brain shift is usually minimum. Apart from trying to reduce brain shift, it is important that virtual information from navigation system should be evaluated and adjusted to the real field by the surgeon by himself.

Key words. neuronavigation, brain shift, computer guided surgery

1 Introduction

Development of neuronavigation systems has contributed greatly in the field of minimally invasive neurosurgery. Nowadays, not only the anatomical information but also functional information can be applied into the surgical field by means of neuronavigation. Neuronavigation can help surgeons enormously so far as the information is correct. Indeed, incorrect usage would destroy both patients and surgeons. In this paper, some tips for correct use of navigation are presented.

2 Institutional Experiences

Since late 1990s neuronal navigation systems have introduced in our institution. Our concept using navigation system is always to combine surgical microscope and navigation system in order not to interfere surgical procedure. Focus point of the micro-

Department of Neurosurgery, Kobe University Graduate School of Medicine, 7-5-1 Kusunoki-cho, Chuo-ku, Kobe 650-0017, Japan

scope is used as a pointer of the navigation system so that surgical field is continuously corresponded to MRI or CT pictures. Important anatomical structures such as tumor boundary or major arteries are traced on the MRI images and superimposed into the microscope field. In this way, surgeons can concentrate on the surgical field without turning their eyes from the microscope to the computer monitor. Firstly a robotic microscope (Zeis-MKM microscope, Carl Zeiss, Oberkochen, Germany) was installed and now we use an optical (infra-red) navigation system (StealthStation TREON plus, Medtronic Navigation Inc., Louisville, CO, U.S.A.) combining with a surgical microscope (OPMI Neuro/NC4, Carl Zeiss, Oberkochen, Germany). Till now, over 200 patients were operated using navigational microscopes.

3 Indication of Navigation

We are now using the navigational microscope especially in cases of pituitary tumors, gliomas, and deep-seated tumors. We have found also usefulness in education and interdisciplinary surgery. One can realize where surgeon is and discuss how he should

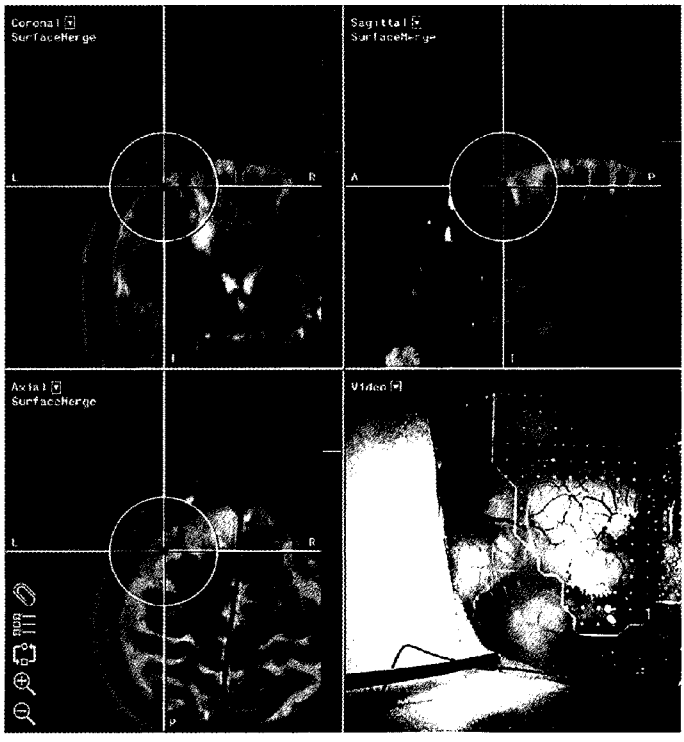


FIG. 1. Screen-shot image of intraoperative navigation in a case of left frontal glioma. After dural opening, cerebral surface was glued to the dural edge with a small amount of fibrin glue in order to minimize brain shift. Tumor boundary is correctly displayed (right lower picture). Focus point of the microscope is displayed three-dimensionally in MRI pictures

further go. Surgery for recurrence is another good indication of neuronavigation. Anatomical landmark is usually difficult to find and further more there is less brain shift owing to adhesion.

Navigational information should be correct. Required accuracy is different in various types of surgery and at various points during surgery. Recent systems can provide easy and accurate registration. Calculated registration error is about 1 or 2 mm. Navigation is very useful at incision. Required accuracy is not so high and there is no brain shift. Tumor margin can be displayed over the skin and one can design accurate and minimum skin incision and craniotomy without experiences.

4 Brain Shift

Once dura is opened, brain shift can take place. Significant shift will happen at the surface area when large cyst is collapsed or much CSF is aspirated. Navigational information should be carefully evaluated at the end of surgery as there is usually great degree of brain shift.

Main problem during surgery is how to cope with this brain shift. One should be aware of and correct the error with his experience and or other information. Anatom-

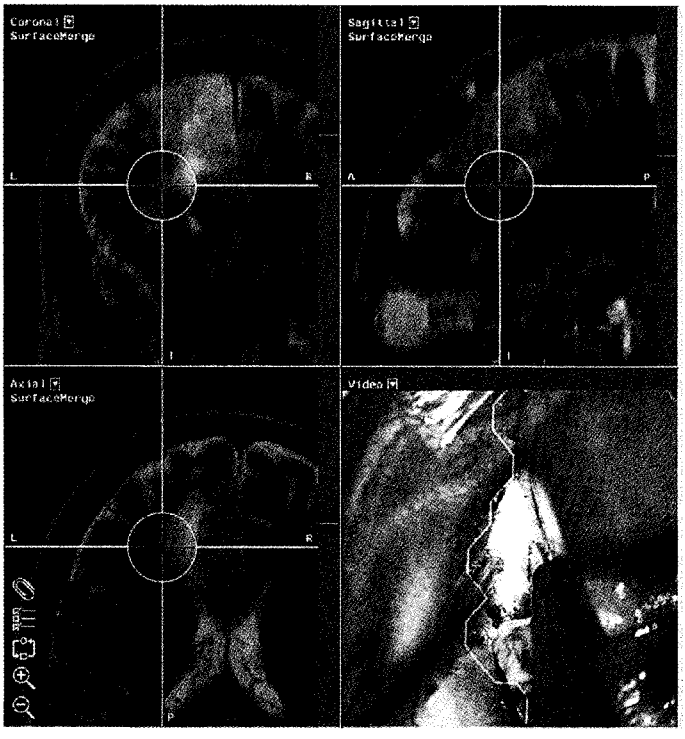


FIG. 2. Continuing to Fig. 1, tumor border was followed by opening the sulcus and further into the white matter from the bottom of the sulcus

ical landmark is useful, once it is identified. One can check the accuracy of the navigation and realize the error by calibrating the anatomical landmarks of computer images to those in the real field. Virtual information from navigation system should be adjusted to the real field by the surgeon. Displayed tumor margin by navigational system should be corrected by surgeon using difference of color and consistency under the microscope. Recently 5-ALA fluorescence can be adjunctively used for malignant tumors to define tumor margin.

5 Gluing Technique

We have found that there is least brain shift in cases with recurrent tumors. Adhesion of brain surface to the dura prevents possible shift during surgery. This taught us an idea to glue the brain surface to the dura at the initial stage. Figures show the effectiveness of this method. A left frontal low-grade glioma was operated using neuronavigation system. Immediately after opening of dura, cerebral surface was glued to the dural edge with a small amount of fibrin glue in order to minimize brain shift. Tumor boundary is correctly displayed and sulcus was opened at the boundary (Fig. 1).

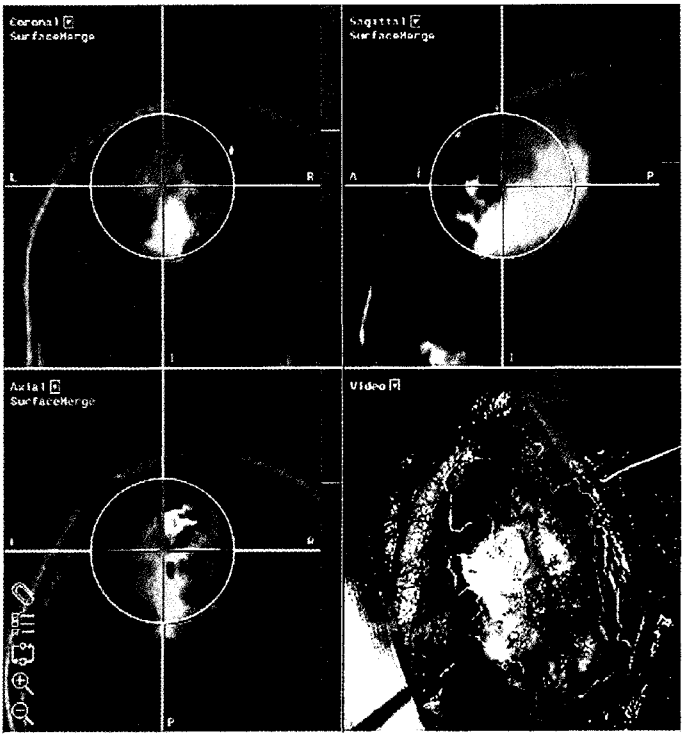


FIG. 3. After removal of the tumor mass, tumor boundary displayed by the navigation (right lower picture) was well matched to the real surgical field. Focus point of the microscope is placed at the middle depth of tumor location. Brain shift was prevented by the gluing technique

Tumor border was followed from the bottom of the sulcus into the white matter (Fig. 2). Tumor was removed with en-bloc manner. After removal of the tumor mass, tumor border displayed by the navigation was well matched to the real surgical field (Fig. 3).

6 Conclusions

We should remember that navigation is not always correct. Apart from mechanical error, brain shift takes place to some extent even if we take care of. Virtual information from navigation system should be adjusted to the real field by the surgeon. Navigation is a tool and surgeon should use it correctly.

Image-Guided Surgery for Gliomas

Hiroki Namba[1], Tsutomu Tokuyama[1], Naoki Yokota[1], Naoto Sakai[2], Tokutaro Tanaka[2], Seiji Yamamoto[3], Susumu Terakawa[3], Baigalmaa Tsagaan[4], and Keiichi Abe[4]

Summary. Standard therapy for gliomas consists of maximum tumor resection and conventional external radiotherapy with/without nitrosourea-based chemotherapy. Recent advances in neuroimaging and intra-operative monitoring techniques enable us to maximize tumor resection with minimum post-operative morbidity even when the tumors locate near the eloquent brain regions. In our institutions, fusion images of MRI and methionine uptake determined by positron emission tomography are prepared pre-operatively. Functional brain regions are mapped using functional MRI, tractography, and occasionally, subdural grid electrode placement. Then, the area of methionine uptake is removed as much as possible using a neuronavigation system and intra-operative functional monitoring with cortical and subcortical stimulations. Awake craniotomy is sometimes used. Intra-operative correction for brain shift during surgery due to brain retraction and cerebrospinal fluid leakage is an important issue. Intra-operative CT and MRI are useful to update informations for neuronavigation but they cost a lot. We have been testing the possibility of more precise and less expensive brain shift correction by combining optical imaging of brain surfaces and ultrasound information of deep structures during surgery.

Key words. glioma, image-guided surgery, intra-operative monitoring, neuronavigation, positron emission tomography

[1] Department of Neurosurgery and [3] Photon Medical Research Center, Hamamatsu University School of Medicine, 1-20-1 Handayama, Hamamatsu 431-3192, Japan,[2] Department of Neurosurgery, Seirei Hamamatsu General Hospital, Sumiyoshi, Hamamatsu, Japan, and [4] Faculty of Computer Science and Information, Shizuoka University, Jouhoku, Hamamatsu, Japan

1 Introduction

The significance of the extent of surgical resection on the prognosis of glioma still remains controversial even at the present time with modern computerized surgical facilities. Low-grade tumors are in general relatively slow-growing and most tumors remain stable for a quite long period even after partial resection with/without radiotherapy. Glioblastoma multiforme, the most malignant histological type of gliomas, on the other hand, is highly invasive and virtually incurable even after removal of the whole tumor mass with contrast-enhancement on MRI. The median survival of the patients with glioblastoma is generally less than one year from the time of diagnosis and this has not significantly improved for more than three decades despite continuous refinement of treatment strategies. Since the tumor recurrence usually occurs from the resection border where some residual tumor cells have been left behind and distant metastasis is seldom observed in gliomas, local tumor control would prolong the survival of those patients. Continuous efforts have been paid to develop novel strategies and some promising experimental data have been demonstrated. Therefore, when the effective adjuvant therapies after surgical removal become available, the extent of surgical removal would become one of the most important prognostic factors, which is already the case in medulloblastoma. In the present paper, current standard therapies for gliomas are reviewed and newly developed methods to improve extent of tumor removal are introduced.

2 Standard Therapy for Gliomas

The recommended therapy for high-grade gliomas is maximum tumor resection followed by conventional external radiotherapy of 54–60 Gy to 2 cm margin of the tumor with/without nitrosourea-based chemotherapy. Chemotherapy with a combination of procarbazine, vincristin, and nitrosoureas is strongly recommended for tumors having oligodendroglial components. For low grade gliomas, no additional therapies have been proven to be beneficial after maximum tumor resection.

2.1 Surgical Resection

The purposes of tumor resection are to make a histological diagnosis and to improve symptoms caused by tumor compression, but the significance of the extent of surgical resection on the prognosis of glioma patients still remains controversial. A recent retrospective analysis of 416 consecutive patients with histologically proven glioblastoma multiforme has shown that extent of tumor resection (<98%), as well as patient age (≥65 years), preoperative performance status (<80%), and tumor location (in the eloquent brain), is a predictor of the shorter survival duration [1]. A significant survival advantage was associated with resection of 98% or more of the tumor volume (median survival 13 months) compared with resection less than 98% (8.8 months).

The influence of extent of tumor resection on survival of patients with low-grade glioma has been also studied [2–4]. Significant unfavorable prognostic factors for survival were age (≥40 years), astrocytoma histology subtype, largest diameter of the tumor (≥6 cm), tumor crossing the midline, and presence of neurological deficit before

surgery. Extensive tumor excision (90% to 100% tumor excised) had a positive effect on survival ($P = 0.046$) [3]. The report of brain tumor registry of Japan also showed that 5-year survivals of low-grade glioma patients with total tumor removal, ≥95%, ≥75%, ≥50% removal, and biopsy were 88.5, 75.4, 64.7, 60.7, and 54.9%, respectively [5].

2.2 Radiation Therapy

It has been proven that radiotherapy significantly improves the survival of patients with malignant gliomas [6]. The median survivals of patients who received no radiation, ≤45, ≤50, ≤55, and ≤60 Gy were 18.0, 13.5, 28.0, 36.0, and 42.0 weeks, respectively. Therefore, post-operative radiotherapy should be delivered for patients with malignant glioma.

Radiation induced toxicities, including dementia and radiation necrosis, are of particular concern in patients with low-grade gliomas because they survive long [7]. A recent randomized trial revealed that irradiation (54 Gy in 6 weeks) significantly improved time to progression but not overall survival in adults with cerebral low-grade glioma [8]. Another recent study showed that low-dose radiation therapy (50.4 Gy in 28 fractions) had somewhat better 2- and 5-year survival (94% and 72%) than high-dose one (64.8 Gy in 36 fractions, 85% and 64%) in adults with supratentorial low-grade glioma [9]. Therefore, a recommended radiation dose for low-grade glioma is 50.4 Gy.

2.3 Chemotherapy

Recent advances in chemotherapy, especially in combination with radiotherapy, have improved the prognosis of many malignant brain tumors including medulloblastoma, malignant lymphoma, and germ cell tumors. However, no breakthrough has come in chemotherapy for malignant gliomas except those with oligodendroglial differentiation. For oligodendroglial tumors, a combination chemotherapy with procarbazine, vincristin, and nitrosoureas (CCNU, ACNU, MCNU) is strongly recommended [10]. For astrocytic tumors without oligodendroglial components, no chemotherapeutic regimens have been proven to be beneficial with strong evidences. Since an increase in 1-year survival of 6% (from 40% to 46%) has been reported in a meta-analysis of nitrosourea-based chemotherapies, nitrosoureas have been usually used [11]. A recent randomized trial in glioblastoma showed an increase in median survival from 12.1 months with radiation alone to 14.6 months with radiation plus temozolomide [12]. Since this new alkylating agent can be orally administered without serious side effects, temozolomide may become the first-line agent for glioblastoma in the near future.

3 Image-guided Resection of Gliomas

When effective post-operative local therapies such as gene therapy become available in the near future, extent of tumor resection may become one of the most important prognostic factors. Therefore, every effort should be made to remove as much tumor as possible without causing neurological deficits.

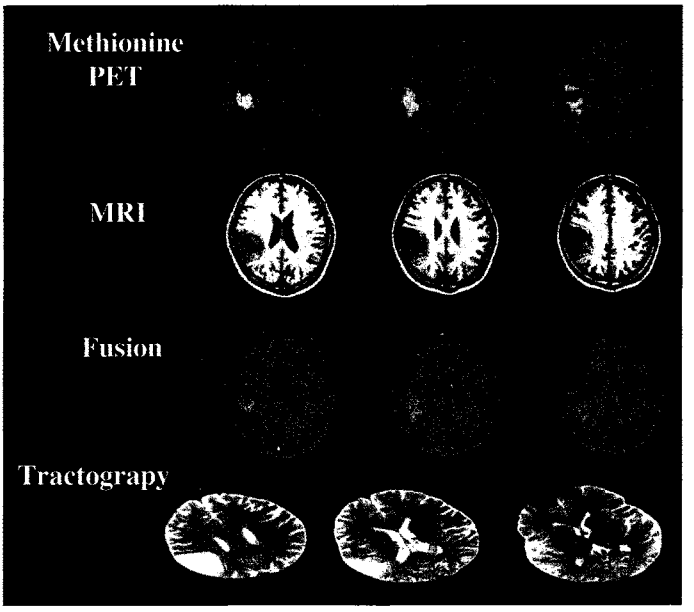


FIG. 1. Positron emission tomography (PET) with L-[methyl-^{11}C]methionine and MR tractography of a patient with right parietal low-grade glioma. Methionine-PET images, corresponding MRIs, and the fusion images of MET-PET and MRI are shown in the top three rows and MR tractography, in the bottom row

3.1 Pre-operative Neuroimaging

Recent advances in pre-operative neuroimaging and intra-operative monitoring techniques enable us to maximize tumor resection with minimum post-operative morbidity. As a pre-operative "tumor imaging", we use positron emission tomography with L-[methyl-^{11}C]methionine as well as conventional MRI (Fig. 1) [13]. Functional MRI and tractography are used for "Functional brain imaging" (Fig. 1). By using these informations and an intra-operative neuronavigation system, maximum resection of regions with methionine uptake without serious neurological deficits becomes possible. Recently, we also use a trans-cranial magnetic stimulation linked with a neuronavigation system for pre-operative evaluation of eloquent brain regions. Motor responses such as finger twitch and speech arrest-like response can be brought about by stimulating certain areas of the cortex.

3.2 Intra-operative Functional Monitoring and Tumor

Using intra-operative functional monitoring with cortical and subcortical stimulations, tumors are removed as much as possible using a neuronavigation system until motor responses to the stimulations are observed. Awake craniotomy is sometimes used especially when removing tumors near the speech function-related brain areas.

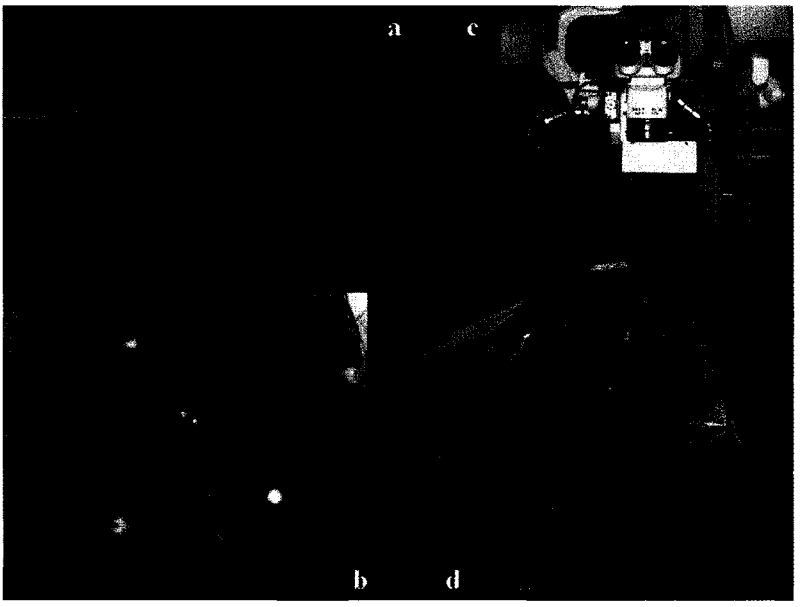


FIG. 2. Real-time brain shift correction by using optical imaging of brain surfaces. A 3-dimentional scanner image (**a**) and a CCD image (**b**) are obtained using a microscope equipped with a laser scanner (**c**). Then we perform real-time remodeling of the pre-operative MRI during surgery by using the informations from shift of brain surfaces (surface scanner) and shift of deep structures (ultrasound data) (**d**)

Intra-operative tumor imaging is also possible using photosensitizers such as 5-aminolevulinic acid (5-ALA). This technique is known as intra-operative chemical navigation. Recently, we are investigating a new photosensitizer, ATX-S10•Na (II), in photodynamic diagnosis as well as photodynamic therapy for glioma [14].

3.3 Correction for Brain Shift during Tumor Removal

Intra-operative correction for brain shift during surgery due to brain retraction and cerebrospinal fluid leakage is an important issue. Intra-operative CT and MRI are used to update informations of the neuronavigation system in some institutions. Intra-operative MRI is obviously the best way for real-time brain shift correction, but the cost is enormous [15]. Intra-operative real-time correction of brain shift using an ultrasound devise is another less-expensive method [16].

Recently we have been testing the possibility of real-time brain shift correction by combining optical imaging of brain surfaces and ultrasound information of deep structures during surgery. Based on these data, we are developing an algorithm for remodeling the preoperative MRI to show brain structures for real-time neuronavigation (Fig. 2).

4 Conclusions

Since most gliomas locally recur, maximum tumor resection using modern imaging facilities at the initial treatment will improve the prognosis of glioma. A considerable number of low-grade gliomas recur, even after long-time tumor dormancy, close observation with MRI is necessary. At the time of recurrence, a second resection with image-guidance should be considered because prolonged survival by repeated resection has been expected.

Acknowledgement. The work was partially supported by the grant "Knowledge Cluster Initiative, Super-visual Imaging Technology to Support Next-Generation Industries and Medical Treatment" from Japanese Ministry of Education, Culture, Sports, Science and Technology.

References

1. Lacroix M, Abi-Said D, Fourney DR, et al (2001) A multivariate analysis of 416 patients with glioblastoma multiforme: Prognosis, extent of resection, and survival. J Neurosurg 95:190–198
2. Keles GE, Lamborn KR, Berger MS (2001) Low-grade hemispheric gliomas in adults: A critical review of extent of resection as a factor influencing outcome. J Neurosurg 95:735–745
3. Pignatti F, van den Bent M, Curran D, et al (2002) Prognostic factors for survival in adult patients with cerebral low-grade glioma. J Clin Oncol 20:2076–2084
4. Johannesen TB, Langmark F, Lote K (2003) Progress in long-term survival in adult patients with supratentorial low-grade gliomas: A population-based study of 993 patients in whom tumors were diagnosed between 1970 and 1993. J Neurosurg 99:854–862
5. Report of brain tumor registry of Japan (1969–1996) (2003). Neurol Med Chir (Tokyo) 43 (Suppl):1–111
6. Walker MD, Strike TA, Sheline GE (1979) An analysis of dose-effect relationship in the radiotherapy of malignant gliomas. Int J Radiat Oncol Biol Phys 5:1725–1731
7. Brown PD, Buckner JC, O'Fallon JR, et al (2003) Effects of radiotherapy on cognitive function in patients with low-grade glioma measured by the folstein mini-mental state examination. J Clin Oncol 21:2519–2524
8. Karim AB, Afra D, Cornu P, et al (2002) Randomized trial on the efficacy of radiotherapy for cerebral low-grade glioma in the adult: European Organization for Research and Treatment of Cancer Study 22845 with the Medical Research Council study BRO4: An interim analysis. Int J Radiat Oncol Biol Phys 52:316–324
9. Shaw E, Arusell R, Scheithauer B, et al (2002) Prospective randomized trial of low-versus high-dose radiation therapy in adults with supratentorial low-grade glioma: Initial report of a North Central Cancer Treatment Group/Radiation Therapy Oncology Group/Eastern Cooperative Oncology Group study. J Clin Oncol 20: 2267–2276
10. Cairncross JG, Macdonald DR (1991) Chemotherapy for oligodendroglioma. Progress report. Arch Neurol 48:225–227
11. Stewart LA (2002) Chemotherapy in adult high-grade glioma: A systematic review and meta-analysis of individual patient data from 12 randomised trials. Lancet 359:1011–1018
12. Stupp R, Mason WP, van den Bent MJ, et al (2005) Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 352:987–996

13. Derlon JM, Petit-Taboue MC, Chapon F, et al (1997) The in vivo metabolic pattern of low-grade brain gliomas: A positron emission tomographic study using 18F-fluorodeoxyglucose and 11C-L-methylmethionine. Neurosurgery 40:276–287
14. Yamamoto J, Hirano T, Li S, et al (2005) Selective accumulation and strong photodynamic effects of a new phtotsensitizer, ATX-S10•Na(II), in experimental malignant glioma. Int J Oncology 27:1207–1213
15. Nimsky C, Fujita A, Ganslandt O, et al (2004) Volumetric assessment of glioma removal by intraoperative high-field magnetic resonance imaging. Neurosurgery 55:358–370
16. Keles GE, Lamborn KR, Berger MS (2003) Coregistration accuracy and detection of brain shift using intraoperative sononavigation during resection of hemispheric tumors. Neurosurgery 53:556–562

Recent Advances in Radiosurgery for Cerebral Arteriovenous Malformations: The University of Tokyo Experience

KEISUKE MARUYAMA, MASAHIRO SHIN, and TAKAAKI KIRINO

Summary. Stereotactic radiosurgery has been widely applied to treat cerebral arteriovenous malformations (AVMs), and various relevant studies have been reported to date. Recently, however, a lot of new facts were clarified by our up-to-date long-term follow-up study after stereotactic radiosurgery using a gamma knife. The risk of hemorrhage from AVMs was reduced by 54% even during the latency period after radiosurgery and further 78% after obliteration. However, a small risk of hemorrhage still remained after obliteration. Therefore, angiographic obliteration, which was one the treatment goals, does not necessarily mean an ultimate cure of AVMs. Such a risk was significantly related to the continuous enhancement on computerized tomographic or magnetic resonance imaging. Advancement in imaging technique provided by these three-dimensional imaging realized significantly less frequent complication. Integration of diffusion-tensor tractography into treatment planning of radiosurgery enabled clear visualization of the corticospinal tract during the treatment planning, and the tolerable dose of the corticospinal tract was clarified to be 25 Gy. Thus, safer and more effective treatment can be achieved with recent advances in stereotactic radiosurgery to treat cerebral AVMs.

Key words. arteriovenous malformation, hemorrhage, gamma knife, obliteration, stereotactic radiosurgery

1 Introduction

Cerebral arteriovenous malformations (AVMs) frequently arise in the younger population and can cause severe disabilities or death [1–3]. Intracranial hemorrhage is the most common clinical presentation, and annual hemorrhage rate is reported to be 2

Department of Neurosurgery, The University of Tokyo Hospital, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan

to 4% during the natural course of the disease [3–9]. Various treatments have been developed in an attempt to reduce the risk of hemorrhage. Stereotactic radiosurgery, in particular, has been widely used as one of the minimally invasive therapies during the past two decades [1–3,10–13]. It provides an angiographic cure in 80 to 95 percent of patients with a latency period of 3 to 5 years [1,14–17]. A lot of relevant studies have been reported to date all over the world. Recently, however, a lot of new facts were clarified by our up-to-date long-term follow-up study after stereotactic radiosurgery using a gamma knife (Elekta instruments, Norcross, GA, U.S.A.) during the past 15 years. Hereby we introduce several recent advances in both knowledge and technique.

2 Diagnosis of Obliteration

2.1 Factors Affecting Obliteration

Several factors affecting successful obliteration were previously reported from multiple centers. We also found that prior hemorrhage, smaller AVM diameter, and higher margin dose were significantly associated with successful obliteration of AVMs by using multivariate logistic regression analysis [18]. In addition, we recently found several factors that significantly associated with earlier obliteration of AVMs; these were male sex, prior hemorrhage, smaller AVM diameter, and treatment planning using biplane angiography alone [18]. This finding indicates that current application of computerized tomography (CT) or magnetic resonance (MR) images into treatment planning is making the process of obliteration slower. In the two-dimensional treatment planning method by using angiography alone, the whole AVM nidus had to be covered extensively within the prescribed isodose line by estimating hidden parts of the lesion behind the projected images of biplanar angiograms. Therefore, in such cases, some parts of the AVM margin may have received a higher dose of radiation than that applied to the margin and this could have led to shorter latency intervals [18]. Based on this result, we have to wait for a longer period than ever until complete obliteration of an AVM.

2.2 Diagnostic Value of Angiography

When compared with the result of angiography, diagnosis of obliteration on CT had 13% of false-negative result, and 20% by means of MR imaging [18]. On the other hand, all of the CT and MR imaging that showed the residual AVM nidus agreed with the result of angiography. Hence, a residual AVM nidus can be diagnosed by means of CT or MR imaging, and angiography to confirm obliteration can be delayed until obliteration is suggested by these less invasive imaging studies. At the same time, however, angiography still remains to be the gold standard to diagnose obliteration of AVMs after radiosurgery.

3 The Risk of Hemorrhage after Radiosurgery

3.1 The Risk of Hemorrhage until Obliteration

Previous studies have reported that the risk of hemorrhage during the latency period (the interval between radiosurgery and obliteration) either decreases [19,20], remains unchanged [21,22], or even increases [10,23] compared to the natural course of the disease. Such comparisons tend to contain selection biases because the patients who underwent radiosurgery were highly selected. Because even the smallest remnant of an AVM constitutes a risk of further hemorrhage [24], it has commonly been assumed that radiosurgery does not protect against hemorrhage unless obliteration is verified (Fig. 1, a gray line) [2]. However, previous studies have not statistically compared the risk of hemorrhage before and after radiosurgery.

Based on our analyses of 500 patients who underwent radiosurgery at our institute, the risk of hemorrhage from AVMs was reduced by 54% even during the latency period after radiosurgery (Fig. 1, a bold line) [25]. Two factors could have potentially caused an underestimation of the risk of hemorrhage during this period. The first was natural decline in the repeated hemorrhage rate from ruptured AVMs [4,5,26,27]. However, no such natural decline was detected in our series [25]. Furthermore, the observed protective effect persisted even in an analysis that excluded data obtained during the first year after diagnosis. Therefore, natural regression of the risk of hemorrhage did not seem to affect our result. The second potential problem was false

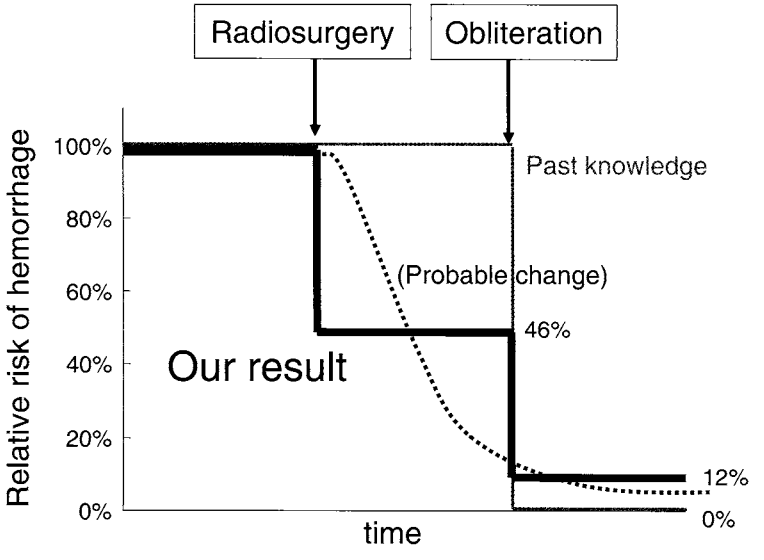


FIG. 1. Schematic changes in the relative risk of hemorrhage after radiosurgery for cerebral arteriovenous malformations. A *gray line* shows past knowledge on the risk of hemorrhage after radiosurgery that was thought as "all or none". A *bold line* indicates the result of our recent study. A *dotted line* demonstrates a probable change in the risk of hemorrhage based on our recent study

extension of the latency period because of a delay in confirming obliteration using cerebral angiography [21,22]. This might have been as long as 6 months, because angiography was only performed after obliteration was suggested using less-invasive imaging carried out at 6-month intervals. However, similar results were obtained when we repeated our analysis adjusting for the delay, which suggested that delayed confirmation of obliteration did not have a significant effect on the results. Thus, even after adjustment for these two potential confounding factors, the protective effect against hemorrhage persisted during the latency period.

Histopathological examinations of AVMs after radiosurgery suggest potential mechanisms by which the risk of hemorrhage may be reduced even before angiographic obliteration. After radiosurgery, the proliferation of smooth-muscle cells forming an extracellular matrix causes progressive thickening of the intimal layer, leading to stenosis and the eventual occlusion of the vessels [28]. This thickening of the intimal layer begins as early as 3 months after irradiation of the vessels [29]. When the thickness of a vessel wall increases twofold, the tangential stress decreases by half according to Karlsson et al [19]. Therefore, thickening of the irradiated vessel walls would decrease the stress after radiosurgery [19]. Second, partial or complete thrombosis of the irradiated vessels, which is one of the pathological changes that occurs after radiosurgery, might decrease the number of patent vessels in AVMs [30]. Third, and finally, in vessels with a smaller diameter, thickening of the endothelium might cause occlusion at a relatively earlier stage, which would decrease the blood flow through AVMs. All three factors might contribute to the protective effect observed.

3.2 The Risk of Hemorrhage after Obliteration

Most previous studies assumed that angiographic obliteration was the ultimate goal of radiosurgery [2,11,12,31], but we recently encountered several cases who suffered from hemorrhage even after angiographic obliteration [32]. Although the risk of hemorrhage from AVMs was reduced by further 78% after obliteration as compared with the latency period [25], a small risk of hemorrhage still remained after obliteration. This means that angiographic obliteration does not necessarily mean an ultimate cure of AVMs.

According to the histological examination of the resected AVMs after post-obliteration hemorrhage, we observed small endothelial cell-lined channels containing erythrocytes within the hyalinization, and some of the AVM vessels were still patent partially, while the majority of the vessels were obliterated as a result of thickening of the intimal layer with dense hyalinization. Hemorrhage might be caused by these microscopically patent vessels, whose diameter was under the threshold of detection using angiography. In other words, if the blood flow through AVMs declines below the threshold of detection using angiography, AVMs will in effect become invisible, although they are still evident histologically [32,33]. In a clinical situation, meanwhile, confirming obliteration by means of angiography is the only way to identify a substantial reduction of the blood flow. It is important to note that an angiogram might only reveal a specific process at a certain time point in the sequence of pathological changes that occur after radiosurgery for AVMs (Fig. 1, a dotted line).

Such a risk of hemorrhage from obliterated AVMs after radiosurgery was significantly related to the continuous enhancement on CT or MR imaging [32]. So, the risk

of hemorrhage after obliteration should be evaluated based on the results of angiography, CT or MR images, and their combination.

We could not detect significant reduction in the risk of hemorrhage from unruptured AVMs, even after obliteration. One possible explanation for this result is that the number of patients without hemorrhage at presentation might not have been sufficient to confirm a subtle decrease in the risk of hemorrhage after radiosurgery and obliteration, because the result would be significant if a patient population was four times larger. Further studies involving larger populations and longer observation periods will be necessary to clarify the protective effect in unruptured AVMs.

4 The Risk of Complication

4.1 Factors Affecting Complication

Several factors affecting the risk of complication were previously reported from multiple centers; the largest factors included treatment volume and margin dose. We recently found that treatment planning using biplane angiography alone was significantly related to neurological deterioration after radiosurgery in multivariate logistic regression analysis as well as AVMs fed by the medial striate artery or the artery of Heubner and sensory disturbance at radiosurgery [18]. This means advancement in imaging technique provided by the three-dimensional CT or MR imaging realized significantly less frequent complication with similar obliteration rates [18].

4.2 Integration of Corticospinal Tractography

We recently integrated three-dimensional corticospinal tractography obtained from diffusion-tensor MR imaging into treatment planning of gamma knife radiosurgery [34]. It realized clear visualization of the corticospinal tract during the treatment planning, and the tolerable dose of the corticospinal tract was calculated to be 25 Gy [34].

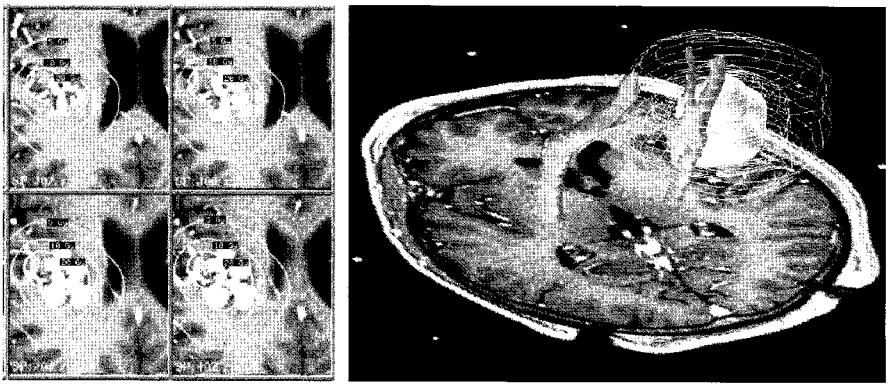


FIG. 2. Radiosurgical dosimetry obtained in a 53-year-old man with an arteriovenous malformation adjacent to the corticospinal tract. The dose to the corticospinal tract was clearly demonstrated after the integration of diffusion-tensor-based tractography

By using this technique and knowledge, we can deliver a sufficiently effective dose to targeted lesions while minimizing the risk of complications even in the treatment of critically located AVMs. This novel technique is highly useful and holds a wide variety of future application in the field of radiosurgery (Fig. 2).

5 Conclusions

By recent advances in both knowledge and technique, safer and more effective treatment can be realized in stereotactic radiosurgery to treat cerebral AVMs. On the other hand, it is important to note that angiographic obliteration, which was one the treatment goals, does not necessarily mean an ultimate cure of AVMs. An angiogram might only reveal a specific process at a certain time point in the sequence of pathological changes that occur after radiosurgery for AVMs.

References

1. Fleetwood IG, Steinberg GK (2002) Arteriovenous malformations. Lancet 359:863–873
2. Ogilvy CS, Stieg PE, Awad I, et al (2001) AHA Scientific Statement: Recommendations for the management of intracranial arteriovenous malformations: A statement for healthcare professionals from a special writing group of the Stroke Council, American Stroke Association. Stroke 32:1458–1471
3. The Arteriovenous Malformation Study Group (1999) Arteriovenous malformations of the brain in adults. N Engl J Med 340:1812–1818
4. Graf CJ, Perret GE, Torner JC (1983) Bleeding from cerebral arteriovenous malformations as part of their natural history. J Neurosurg 58:331–337
5. Itoyama Y, Uemura S, Ushio Y, et al (1989) Natural course of unoperated intracranial arteriovenous malformations: Study of 50 cases. J Neurosurg 71:805–809
6. Brown RD Jr, Wiebers DO, Forbes G, et al (1988) The natural history of unruptured intracranial arteriovenous malformations. J Neurosurg 68:352–357
7. Brown RD Jr, Wiebers DO, Torner JC, et al (1996) Frequency of intracranial hemorrhage as a presenting symptom and subtype analysis: A population-based study of intracranial vascular malformations in Olmsted County, Minnesota. J Neurosurg 85:29–32
8. Crawford PM, West CR, Chadwick DW, et al (1986) Arteriovenous malformations of the brain: Natural history in unoperated patients. J Neurol Neurosurg Psychiatry 49:1–10
9. 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
10. Steinberg GK, Fabrikant JI, Marks MP, et al (1990) Stereotactic heavy-charged-particle Bragg-peak radiation for intracranial arteriovenous malformations. N Engl J Med 323:96–101
11. Lunsford LD, Kondziolka D, Flickinger JC, et al (1991) Stereotactic radiosurgery for arteriovenous malformations of the brain. J Neurosurg 75:512–524
12. Steiner L, Lindquist C, Adler JR, et al (1992) Clinical outcome of radiosurgery for cerebral arteriovenous malformations. J Neurosurg 77:1–8
13. Maruyama K, Niranjan A, Kondziolka D, et al (2004) Stereotactic radiosurgery for brainstem arteriovenous malformations: Factors affecting outcomes. J Neurosurg 100:401–407

14. Shin M, Kawamoto S, Kurita H, et al (2002) Retrospective analysis of a 10-year experience of stereotactic radiosurgery for arteriovenous malformations in children and adolescents. J Neurosurg 97:779–784
15. Karlsson B, Lindquist C, Steiner L (1997) Prediction of obliteration after gamma knife surgery for cerebral arteriovenous malformations. Neurosurgery 40:425–431
16. Colombo F, Pozza F, Chierego G, et al (1994) Linear accelerator radiosurgery of cerebral arteriovenous malformations: An update. Neurosurgery 34:14–21
17. Friedman WA, Bova FJ, Mendenhall WM (1995) Linear accelerator radiosurgery for arteriovenous malformations: The relationship of size to outcome. J Neurosurg 82:180–189
18. Shin M, Maruyama K, Kurita H, et al (2004) Analysis of nidus obliteration rates after gamma knife surgery for arteriovenous malformations based on long-term follow-up data: The University of Tokyo experience. J Neurosurg 101:18–24
19. Karlsson B, Lindquist C, Steiner L (1996) Effect of Gamma Knife surgery on the risk of rupture prior to AVM obliteration. Minim Invasive Neurosurg 39:21–27
20. Levy RP, Fabrikant JI, Frankel KA, et al (1989) Stereotactic heavy-charged-particle Bragg peak radiosurgery for the treatment of intracranial arteriovenous malformations in childhood and adolescence. Neurosurgery 24:841–852
21. Pollock BE, Flickinger JC, Lunsford LD, et al (1996) Hemorrhage risk after stereotactic radiosurgery of cerebral arteriovenous malformations. Neurosurgery 38:652–661
22. Friedman WA, Blatt DL, Bova FJ, et al (1996) The risk of hemorrhage after radiosurgery for arteriovenous malformations. J Neurosurg 84:912–919
23. Fabrikant JI, Levy RP, Steinberg GK, et al (1992) Charged-particle radiosurgery for intracranial vascular malformations. Neurosurg Clin N Am 3:99–139
24. Guo WY, Karlsson B, Ericson K, et al (1993) Even the smallest remnant of an AVM constitutes a risk of further bleeding. Case report. Acta Neurochir (Wien) 121:212–215
25. Maruyama K, Kawahara N, Shin M, et al (2005) The risk of hemorrhage after radiosurgery for cerebral arteriovenous malformations. N Engl J Med 352:146–153
26. Fults D, Kelly DL Jr (1984) Natural history of arteriovenous malformations of the brain: A clinical study. Neurosurgery 15:658–662
27. Mast H, Young W, Koennecke H, et al (1997) Risk of spontaneous haemorrhage after diagnosis of cerebral arteriovenous malformation. Lancet 350:1065–1068
28. Schneider BF, Eberhard DA, Steiner LE (1997) Histopathology of arteriovenous malformations after gamma knife radiosurgery. J Neurosurg 87:352–357
29. Phillips T (1991) Early and late effects of radiation on normal tissues. In: Gutin P, Leibel S, Sheline G (eds) Radiation injury to the nervous system. Raven Press, New York, pp 37–55
30. Chang SD, Shuster DL, Steinberg GK, et al (1997) Stereotactic radiosurgery of arteriovenous malformations: Pathologic changes in resected tissue. Clin Neuropathol 16:111–116
31. Lindquist C, Steiner L (1988) Stereotactic radiosurgical treatment of arteriovenous malformations. In: Lunsford L (ed.) Modern Stereotactic Neurosurgery. Martinus Nijhoff Publishing, Boston, pp 491–505
32. Shin M, Kawahara N, Maruyama K, et al (2005) Risk of hemorrhage from an arteriovenous malformation confirmed to have been obliterated on angiography after stereotactic radiosurgery. J Neurosurg 102:842–846
33. Yamamoto M, Jimbo M, Kobayashi M, et al (1992) Long-term results of radiosurgery for arteriovenous malformation: Neurodiagnostic imaging and histological studies of angiographically confirmed nidus obliteration. Surg Neurol 37:219–230
34. Maruyama K, Kamada K, Shin M, et al (2005) Integration of three-dimensional corticospinal tractography into treatment planning for gamma knife surgery. J Neurosurg 102:673–677

Intramedullary Spinal Cord Glial Tumours: Management Philosophy and Surgical Outcome

Suresh Nair, Girish Menon, Basrur Ravi Mohan Rao,
Boyini Jagadeeshwara Rajesh, Thiagrajan Muthurethinam,
Abraham Mathew, Hari Venkat Easwer,
and Robindra Nath Bhattacharya

Summary. A retrospective analysis of 88 consecutive cases of intramedullary glial tumours, which constituted 58% of 149 cases of intramedullary lesions surgically managed over a 22-year period, is presented. Fifty-six astrocytomas and 32 ependymomas formed the group, which comprised 55 males and 33 females. While majority of the astrocytomas were in the cervical or cervicodorsal location (70%), it was almost equally distributed between the cervical and conus regions in 23 cases of ependymomas. The management philosophy has changed over the years from biopsy to total removal for ependymomas and a generous inside out decompression in case of astrocytomas. While only a biopsy or decompression was done in 35 of the earlier patients of astrocytomas a radical removal (subtotal in 18 and total in 3) could be achieved in 21 of our recent patients. We could achieve total resection in all the last 17 patients of ependymomas. Low grade astrocytomas radically removed and all ependymomas were not given radiotherapy. Out of the 39 patients of astrocytomas who are in follow up, 13 have improved, 19 remaining static and 7 have deteriorated. While only three of the 25 patients of ependymomas on long term follow up have deteriorated 18 have improved and 6 are remaining static. Conclusion: Although total resection of ependymomas have become a procedure with good functional results in most hands, a radical resection can be achieved with long term stabilisation of neurological deficits in majority of astrocytomas.

Key words. intramedullary, spinal cord, astrocytoma, ependymoma

1 Introduction

Intramedullary tumours of the spinal cord account for 2–4% of CNS neoplasms and about 20–25% of all intraspinal tumours [1]. Intramedullary tumours compromise about one third of spinal neoplasms in adults [2]. Astrocytomas and ependymomas

Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum, 695011, India

account for more than 80% of intramedullary tumours in most series [3]. Until recently their management remained unclear mainly because of the debate regarding the nature and extent of surgery and the relative risks of surgery and radiotherapy in the treatment of these lesions. In many series patients were treated before the advent of modern diagnostic tools and surgical adjuncts and the approach used to be biopsy, dural decompression and radiation therapy based on the assumption that carrying extensive removal of tumours from within the cord was not feasible without inflicting additional neurological insult. As a result the optimal management of this entity remained unclear. With the advent of magnetic resonance imaging and a number of surgical tools such as the operating microscope, ultrasound, ultrasonic tissue aspirator and the laser the diagnosis and management of these lesions have become more easier and safer. Despite these modern advances intramedullary surgery remains a formidable undertaking. However the earlier pessimistic outlook has paved way to optimism over the years ever since the first successful removal of an intramedullary tumour by Von Eiselberg [4]. Greenwood [5,6], Rand [7], Yasergill [8], Stein [9] all were strong proponents in favour of surgery. The most vocal proponent for aggressive surgery in recent years has been Epstein [10–13].

1.1 Materials and Methods

Our experience [14] has ranged from a child of two years of age to a seventy year old male (Tables 1, 2 and 3). But the peak incidence was noted in the third and fourth decade. Astrocytomas and ependymomas were the most common lesions in our study also. Majority of the astrocytomas were located in the cervical region where as the predominant site for ependymomas was in the conus region (Table 4). Almost all patients presented with characteristics features of an intramedullary tumour (Table 5).

The principles of surgical techniques [15] used can be summarised as follows:

TABLE 1. Intamedullary tumours

Type	*n*
Astrocytoma	56
Ependymoma	32
Cavernoma	14
Hemangioblastoma	08
Lipoma	11
Others	28
Total	149

TABLE 2. Intramedullay tumours: Sex distribution

Sex	Astrocytoma (56)	Ependymoma (32)	Others (61)	Total (149)
Male	33	22	36	91
Female	23	10	25	58

TABLE 3. Intramedullary tumours: Age distribution

Age	Astrocytoma (56)	Ependymoma (32)	Others (61)	Total (149)
1–10	05	03	03	11
11–20	12	06	06	24
21–30	11	09	15	35
31–40	16	08	17	41
41–50	08	06	12	26
51–60	03		05	08
61–70	01		03	04

TABLE 4. Intramedullary tumours: Location

Location	Astrocytoma (56)	Ependymoma (32)	Others (61)	Total (149)
Cervical	27	09	20	56
Cervicodorsal	12	04	12	28
Dorsal	11	01	24	36
Dorsolumbar	06	04	03	13
Conus		10	02	12
Filum		04	–	04

TABLE 5. Intramedullary tumours: Clinical presentation

Presentation	*n*	%
Motor weakness	132	88
Pain	56	39
Sensory	104	70
Sphincter	83	59

(1) Full extent of tumour to be exposed with lamninotomy one level above and below the level of the lesion;
(2) Dural opening sparing the arachnoid;
(3) Cord opened through a midline myleotomy or through the most widened avascular part of the cord.
(4) Initially 1–2 cm myelotomy done over the greatest enlargement and to be extended over the entire rostrocaudal limit of the tumour.
(5) Myeleotomy deepened gently by spreading microforceps in longitudinal axis and tumour surface identified.
(6) Both tumour poles identified and polar cysts entered.
(7) Apply pial traction sutures for better visualisation and to provide counter traction for development of dorsal and dorsolateral tumour plane.
(8) Retraction of the tumour done rather than the cord.
(9) Biopsy obtained for histological confirmation.
(10) Dissection done from one end. Internal decompression if tumour is bulky and hinders dissection plane.

TABLE 6. Intramedullary tumours: Type of surgery

Type of surgery	Astrocytoma (56)	Ependymoma (32)	Others (61)	Total (149)
Biopsy	19	05	12	36
Decompression	16	09	21	46
Subtotal	18	01	-	19
Total	03	17	28	48

TABLE 7. Outcome at discharge

Outcome	Astrocytoma (56)	Ependymoma (32)	Others (61)	Total (149)
Improved	07	13	22	42
Static	28	11	25	64
Deteriorated	15	08	12	35
Dead	06	-	02	08

(11) Dissection of the ventral plane done last and supply from anterior spinal vessels are cauterises and divided.
(12) Dura closed primarily or using a dural patch graft.
(13) Useful intraoperative adjuncts include SSEP, intraoperative ultrasonography, CUSA, LASER.

1.2 Surgical Outcome

The early and long term outcome in patients following removal of intramedullary tumour is related to multiple factors including patient age and neurological status, location and histology of the tumour. Young age and a good preoperative neurological grade facilitate good outcome.A trend towards more aggressive surgical removal is evident in our series especially for benign lesions and ependymomas. We had an overall mortality rate of 5.37% (Table 6).

At discharge 20 of our 88 patients (glial tumours) improved in neurological function 39 removed static and 23 deteriorated. The long term outcome following removal of an intramedullary tumours seems to depend on the tumour histology with benign and encapsulated tumours doing well. Of the 64 operated patients with glial neoplasms available for long term follow up, 21 showed improvement, 8 remained static and 25 had deteriorated (Tables 6 and 7).

1.3 Complications

In the immediate post operative period, most patients demonstrate some degree of neurological deficit especially of motor symptoms and posterior column function. These deficits are usually transitory and recover within a few months particularly the motor deficits. Posterior column dysfunction also tends to improve but not to the pre operative level. Sometimes, this dysesthetic syndrome may remain persistive and distressing often causing causalgia like complaints. Other immediate post operative

complications include CSF leak, infection and wound dehiscence especially with dorsal wounds. Late complications include hydrocephalus, post operative spine deformity and anterior subarachnoid CSF loculations.

2 Discussion

2.1 Surgical Anatomy

The spinal cord averages 47 cm in length and 32 g in weight accounting for about 3% of central nervous system. Spinal cord generally occupies less than one-half of the cross sectional area of the spinal canal. It is divided almost into two halves by the anterior median fissure and the posterior median septum. This fissure contains the anterior spinal artery and vein and their penetrating branches and is rarely encountered during surgery. The posterior median septum is composed of fused pia matter from the medial surface of each posterior column. It is the route of entry for removal of most intramedullary pathology and can be identified by a longitudinal array of penetrating vessels. The blood supply to the spinal cord is by way of a single anterior and paired posterior spinal arteries. These vessels are supplemented throughout their course by a variable number of medullary vessels which are well protected on the ventral surface of their respective nerve roots. The intra dural spinal vascular system is well protected and not threatened during intradural surgery. The spinal dura extends as an oval tube from the foramen magnum to the S2 level. It is a tough fibrous membrane composed of longitudinal bundles of collagen and lined one either side by a single layer of flattened fibroblasts. It demonstrates negligible resistance to compression, but has considerable tensile strength. It is under resting tension and possesses elastic properties that allow for folding and unfolding in response to changes in canal length. Spinal dura is an effective barrier and is rarely transgressed by inflammatory or neoplastic pathology. The pia and arachnoid (leptomeninges) are probably neural crest and mesodermal in origin. Arachnoid is a thin transparent membrane which is closely applied to the dura allowing only a potential subdural space. Fenestrated reflections of arachnoid occur through out the subarachnoid space to become continuous with the outer pia. The spinal vasculature is loosely held to the surface of the spinal cord within this layer. The arachnoid reflections also sheath the individual nerve roots. Spinal pia is a well defined collagenous membrane and is thicker than the intracranial pia and it accounts for the white colour and firm consistency of the spinal cord. Lateral reflections of the pia form the dentate ligaments. The pia matter is tightly applied to the outer glial limiting membrane of the spinal cord and completely encircles the cord except at the root entry zones where it is briefly reflected over the exiting nerve roots. It is here that the pia may be transgressed by benign pathology. Benign intramedullary tumours such as ependymoma or astrocytoma may rarely present with an exophytic tumour component which exits the spinal cord through the root entry zone. Centripetal growth of a benign nerve sheath tumour may elevate the pia to become partially subpial in location. In these cases, excision of a segment of pia will be required to affect complete removal. Intramedullary lesions may be categorized according to their relationship with the cord.

These lesions may be purely intramedullary, subpial or pial based or exophytic. Intramedullary tumours comprise about one-third of spinal neoplasms in adults. Astrocytomas and ependymomas represent more than 80% of intramedullary tumour lesions in most series. A variety of other lesions account for the rest twenty percent.

2.1.1 Ependymomas

They originate from rests of ependymal cells in the centre of the spinal cord and appear as a soft red or greyish purple mass with a variable number of vessels crossing the tumour surface. As they grow from their point of origin, they push the adjacent spinal cord aside and therefore are distinct from the surrounding spinal cord and can be dissected from it. If the frozen section report is an ependymoma every attempt is made to remove the tumour in toto. The myelotomy is lengthened and deepened to fully expose the entire rostrocaudal extent of the tumour and should actually continue a few millimetres above and below the tumour margins, allowing greater lateral retraction and visibility while minimizing tension on the spinal cord. Although these tumours are somewhat friable, they are sharply circumscribed and gentle blunt manipulation will not violate the tumour surface. The rostral tumour is frequently rounded and often projects into a cyst which aids in dissection. The caudal pole is usually more tapered since inferior cysts are less common, but there is often a tough fibrous connection between the caudal tumour pole and the central canal. In the absence of a rostral or caudal cyst, the tumour resection is initiated in the middle of the neoplasm which is the most voluminous area. In the presence of a polar cyst, the resection is initiated at the cyst-tumour junction where the interface between the tumour and the normal tissue is easily obtained. The dorsal and lateral margins are established by gentle traction on the tumour against the counter traction provided by the pial sutures. Spreading the microforceps parallel to the long axis of the tumour easily develops the dissection plane, owing to the differences in texture and consistency between the tumour surface and the surrounding gliotic margin of the spinal cord. Feeding vessels and more fibrous attachments are cauterised and divided close to the tumour. The decision to debulk the tumour internally is made once the dorsal half of the tumour is exposed. Although smaller lesions may be removed in one piece, generally the bulk of the tumour should be reduced first. The most important technical point is that there is no effort to carry an en bloc resection. The bulk of the tumour will hinder exact visualisation of the dissection plane requiring prohibitive amounts of spinal cord retraction if one attempts en bloc resection. The dorsal tumour surface is incised and internal decompression is performed with an ultrasonic aspirator. Too much internal tumour removal may cause fragmentation of the tumour surface and obscuration of the correct dissection plane resulting in an undesirable piecemeal removal. As the centrum of the tumour is decored the lateral margins gradually fold in establishing the tumour-cord interface. This cleavage may be accomplished by retraction of the remaining tumour tissue into the residual cavity and not by retraction of spinal cord from the tumour. Dissection of the ventral plane is the most difficult aspect of tumour removal. This is because pial traction sutures do not transmit effective counter traction to the ventral interface between cord and tumour. Also tumour margins appear less distinct and requires sharp dissection techniques.

TABLE 8. Outcome at last follow up

Outcome	Astrocytoma (56)	Ependymoma (32)	Others (61)	Total (149)
Improved	13	18	25	56
Static	07	01	03	11
Deteriorated	19	06	15	40

The anterior median fissure extends almost to the central canal and the tumour is in close approximation to the anterior spinal artery and branches. With superior traction on the tumour directed perpendicular to the long axis of the spinal cord, the tumour can be separated from anterior spinal vessels, which are identified, cauterised and divided. Dissecting the poles of the tumour is more difficult. If a cyst is present, the end of the tumour is obvious. If there is no cyst, the tumour tapers into a root that blends into the central canal of the cord. Following tumour removal, the resection bed is inspected and any bleeding is controlled with warm saline irrigation and application of surgicel. The pial traction sutures are removed and the cord assumes its normal position. No attempt is made to reapproximate the dorsal hemi cords with pial sutures. A watertight dural closure is generally possible in primary operations. In secondary procedures or if closure of dura would in any way narrow the subarachnoid space a dural graft using fascia lata or lumbodorsal fascia or lyophilised cadaver dura is frequently neseesary. Permanent coloured sutures are used because it will provide a midline orientation in case reoperation is required for recurrent tumours. Special attention is paid to the fascial layer as this is usually the watertight layer. Fascia and muscles should be released from the superficial subcutaneous tissues and deep bony elements to achieve closure with no tension. Finally the skin is closed after putting deep and superficial subcutaneous sutures. We could achieve a total excision in seventeen of our total thirty two patients (Table 8) and nearly three fourths of our patients had shown improvement at the time of last follow up (Tables 6 and 7).

2.1.2 Astrocytomas

The surgical treatment of intramedullary astrocytomas remains a much more formidable problem than ependymomas. Adult spinal cord astrocytomas are infiltrating tumours that are histologically similar to intracranial astrocytomas. Usually they are located several millimetres beneath the dorsal surface of the cord and although they may be distinguished by their yellowish grey glossy appearance from the surrounding spinal cord, they blend imperceptibly with the spinal cord at the margins. Many have reported that a radical resection of these infiltrative lesion will result in a higher morbidity and advice only a generous, but limited internal decompression. More radical tumour removal until the establishment of the tumour-cord interface will not alter the clinical course in adults with malignant astrocytoma. However there have been reports of radically resected astrocytomas without increased morbidity. In our experience the surgery on this subgroup of patients has not been always associated with higher postoperative morbidity, but the rate of radical resections has been definitely lower than that for other tumours. Because these malignant astrocytomas recur with in a year independent of amount of resection, we agree that a less radical intervention with

minimal surgical morbidity is the ideal treatment. The lower grade lesions are avascular and lend themselves to radical resection. In children these tumours behave similarly to low grade posterior fossa astrocytomas which are amenable for total resection. After biopsy confirmation of histology an internal decompression is carried out using cavitron. These well circumscribed astrocytomas will often have a well defined dorsal surface plane with white matter but often fade imperceptibly into the gray matter. An "inside-out" removal is recommended and is dictated by surgeon's ability to differentiate clearly, on the basis of colour and consistency, tumour from the surrounding spinal cord. While many low grade astrocytomas have discrete cleavage planes and adjacent cystic components and a fibrillary character on histological examination some have extensive areas with poorly defined interface. In these areas the only guidance to tumour removal is progressive change of colour and tissue consistency. Whenever the tumour comes close or reaches the subpial surface, especially the ventral one, no attempt is made to pursue a radical resection. Although approximately two thirds of all spinal cord astrocytomas in adults are not histologically malignant lesions, they behave in a less-than benign fashion. By virtue of their location and tendency to infiltrate, even small tumours can produce severe neurological deficits. Recurrence after incomplete resection and malignant transformation can occur like their cranial counterparts. The surgical techniques for astrocytomas are similar to ependymomas. Under magnification, the tumour which presents subpially, may be distinguished from the normal spinal cord by colour and texture. By first opening the cyst, the dissection plane can be more readily identified than by trying to attack the tumour-cord interface directly. Pial traction microsutures are as useful in this tumour as with ependymomas. In the presence of a cystic holocord astrocytoma, tumour removal is initiated either at the rostral or caudal pole in the region of tumour-cyst junction. Excision of the solid noncystic astrocytoma is initiated in the mid portion rather than at the rostral or caudal pole of the neoplasm because there is no clear rostral or caudal demarcation of the tumour as occurs in caudal and rostral cysts. The last fragments of the rostral and caudal segments of the tumour are removed by working within the myelotomy and distracting the residual neoplasm into the surgical cavity without extending the myelotomy. Intraoperative ultrasound helps to monitor the progress and clearly identify the rostral and caudal extent of the tumour. Ultrasound also gives a very precise image of the cross sectional image of the tumour cavity and its relationship to the anterior subarachnoid space. Because residual tumour is always present dura is closed with a dural patch to avoid constricting the spinal cord. We could achieve total excision in only three of our patients and in nineteen of them only biopsy was done. Thirty four patients underwent partial to subtotal decompression (Table 8) and nearly thirty patients were send for adjuvant therapy. Outcome was not as favourable as in ependymomas with only one third patients showing some improvement at the time of last follow up (Tables 6 and 7).

3 Management Philosophy of Intramedullary Tumours

It has now been established that long term tumour control or cure can be achieved with acceptable morbidity by microsurgical removal alone for nearly all ependymomas, hemangioblastomas and other well circumscribed lesions which include many

astrocytomas as well. It is the surgeon's intraoperative identification of a tumour/cord interface that is the most important determinant of resectability. Aggressive surgery is of no value for malignant intramedullary tumours and frozen section identification of malignancy signals an end to operation. Conversely if histological identification reveals a benign ependymoma, gross total resection should be the goal even if the margins of the tumour are not immediately evident. So as observed by MCCormick [2,3] it seems reasonable to assume that all patients harbour a benign lesion for which definitive surgical removal is the treatment of choice. If the surgeon intraoperatively after adequate myletomy identifies a clear demarcation from the surrounding spinal cord he should attempt total removal. The effect of radiation therapy on intramedullary spinal cord tumours has not been proven and is obscured by the lack of knowledge of the natural course of these tumours and by the lack of follow up findings confirming the reduction of tumour size after radiation therapy.

The goal of surgery is to remove the tumour totally with preservation or improvement of neurological function. These objectives cannot be always achieved because some tumours infiltrate adjacent neural tissue and make total removal impossible without incurring an unacceptable loss of function. Even when a tumour is well delineated from the normal spinal cord, removal may result in a permanent increase in neurological deficit. The diagnosis of an intramedullary tumour does not necessarily mandate operative removal. The decision to operate on patients with far advanced neurological deficits must be made with realistic expectations. Recovery from a significant long-standing deficit rarely occurs. Neurological outcome is directly related to patients preoperative status. Neurological improvement from a preoperative major deficit can be modest and seen only in a minority of patients. Usually it is the minor deficits which are likely to improve. Thus the major benefits of intramedullary tumour removal is prophylactic. Most patients experience some degree of neurological morbidity in the immediate postoperative period. This brings the issue of managing a patient who presents with neck or back pain with very little objective deficits. Many such patients with minor symptoms and no significant functional impairment are unwilling to risk neurological deterioration as a result of operation. In this situation, the patient should be followed closely for the appearance of additional symptoms or an objective deficit. Once the symptoms progress, patients frequently are more prepared psychologically to face the risks of surgery. There is no therapeutic role for operation in patients harbouring malignant intramedullary tumours because surgery usually results in significant neurological morbidity and also there is the theoretical risk of secondary cerebrospinal fluid dissemination. But preoperative prediction of histology based on MRI scan characteristics alone should be avoided as they are often incorrect and may unfairly influence the surgical objective. So the surgeon should assume that the majority of intramedullary tumours are benign and are potentially resectable. Because ependymomas cannot be distinguished reliably from astrocytomas by their clinical presentation or currently available imaging techniques, all intramedullary spinal cord tumours must be explored aggressively so that curable lesions are not overlooked. An attempt at radical removal should be made according to the gross rather than histologic tumour characteristics because some low grade astrocytomas are also well circumscribed and amenable to radical resection. Histologic interpretation of tiny biopsy fragments obtained through a limited myelotomy

is frequently inaccurate. An inadequate myelotomy may fail to reveal a clear resection plane and histologic interpretation of tumour specimens can result in erroneous tissue diagnosis. It is of paramount importance that surgeon gets a correct tissue diagnosis because under certain circumstances biopsy results define the surgical objective. Frozen section identification of a malignancy signals an end to the operation and no aggressive tumour removal is undertaken. If histological examination clearly demonstrates a benign pathology every attempt should be made for a gross total removal even if the margins of the tumour are not immediately evident to the surgeon.

4 Recurrence and Role of Radiotherapy

Although ependymomas are considered benign by some their glial derivations, lack of capsulation and friable nature pose a risk of recurrence. These lesions are best managed by total removal. We do not recommend radiotherapy after total removal of ependymomas. No efficacy of radiation therapy following grossly complete removal of a spinal ependymomas has been demonstrated and adjuvant radiotherapy is best reserved for patients with malignant ependymomas or a tumour that cannot be resected totally. In an young patients with obvious tumour recurrence who is in good neurological condition, reoperation is the recommended strategy.

Contrary to the finding in children, astrocytomas in adults pursue a progressive course. It seems unlikely that radical tumour removal significantly effects survival. Risk of recurrence is high almost all our patients who came for follow up showing progressive neurological deterioration. Reoperation is best deferred until the patent becomes symptomatic because the interval between MRI and clinical evidence of recurrence may extend several years. Well encapsulated benign lesions who were operated in good neurological state fared better. There is no place for radiotherapy without histological diagnosis or any indications for its use in treating intramedullary tumours except in high grade gliomas which are very rare.

5 Conclusions

Surgical resection of intramedullary tumours should be performed before patient develops substantial deficits. Recovery from significant and long standing deficits rarely occurs. Vast majority of ependymomas as well as a substantial number of low grade gliomas can be radically resected with acceptable morbidity. Partial removal is confined only to cases, which have a clear tendency for infiltration. The gentleness of tissue dissection, the ability of the surgeon to differentiate clearly tumour from the surrounding spinal cord and the ease with which the tumour spinal cord interface is developed obviously influence morbidity.

There is no place for radiotherapy without histological diagnosis or any indications for its use in treating intramedullary tumours except in high grade gliomas which are very rare. In case of recurrence we would recommend operating again. Although the benefits of this philosophy has been well established for ependymomas and other well circumscribed neoplasms, more experience will be required to define long term benefits of radical resection of benign spinal cord astrocytomas.

References

1. Stein BM, McCormick PC (1991) Intramedullary neoplasm and vascular malformations. Clin Neurosurg 39:361–387
2. McCormick PC (1993) Anatomic principles of intradural spinal surgery. Clin Neurosurg 41:204–223
3. McCormick PC, Stein BM (1990) Intramedullary tumours in adults. Neurosurg Clin N Am 3:609–630
4. Mallis L (1960) Intamedullary spinal cord tumours. Clin Neurosurg 17:310–330
5. Greenwood J (1963) Surgical management of intramedullary tumours. J Neurosurg 20:665–668
6. Greenwood J (1967) Surgical removal of intramedullary tumours. J Neurosurg 26:276–282
7. Rand RW (1952) Surgery for multiple intraspinal lesions. J Neurosurg May 9(3): 310–314
8. Yasergill MG (1976) Microsurgical removal of intramedullary hemangioblastoma. Surg Neurol 6:141–148
9. Stein BM (1976) Surgery of intramedullary spinal cord tumour. Clin Neurosurg 26:529–547
10. Epstein F, Lee M, Rezal AR (1995) Intramedullary spinal cord lipomas. J Neurosurg 82:390–400
11. Epstein FJ (1992) Adult intramedullary astrocytoma of the spinal cord. J Neurosurg 77:355–359
12. Epstein FJ (1993) Adult intramedullary spinal cord ependymoma. J Neurosurg 79:205–209
13. Epstein FJ, Epstein N (1981) Surgical management of holocord intramedullary spinal cord astrocytoma in children: Report of 3 cases. J Neurosurg 54:829–832
14. Nair S, Pai KM, Menon G, et al (1997) Management of intramedullary lesions. Prog Clin Neurosci 12:331–343
15. Nair S, Menon G, Parameswaran S, et al (2001) Techniques of removal of intramedullary lesions. Indian Clin Neurosurg 1:178–196

Surgical Tactics for Subaxial Spinal Cord Injury

Junichi Mizuno and Hiroshi Nakagawa

Summary.
Objectives: Surgical tactics for patients with spinal cord injury (SCI) vary in each hospital, because of lack of guidelines for management of SCI. We report our experience of treatment of subaxial SCI.
Patients and methods: Sixty-nine patients who underwent surgical treatments were included from the last 12 years. There were 53 men and 16 women, with age ranging from 16 to 84 years. Nineteen patients developed Frankel A or B quadriparesis. Twenty-five patients with fractures and dislocations had an emergency operation, while 44 patients without bone insults had a delayed operation.
Results: Eight patients of Frankel A or B (38%) showed grade 1 or 2 recovery after an operation, while 4 died of respiratory disturbance within 6 months. Cervical radiographs in flexion-extension studies as well as CT and MRI were useful to evaluate SCI. Myelography was performed in none of cases. No major complications such as vascular or neural damage occurred during an operation. Patients who underwent spinal instrumention started rehabilitation at the early recovery stage.
Conclusions: Dynamic radiological studies are diagnostic for instability. Myelography is considered unnecessary as an examination for evaluating SCI. Spinal instrumentation facilitates early rehabilitation because it avoids a halo brace.

Key words. spinal cord injury, surgery, spinal instrumentation, interfacetal locking, burst fracture

Department of Neurological Surgery, Aichi Medical University, 21 Karimata, Yazako, Nagakute, Aichi-gun, Aichi 480-1195, Japan

1 Introduction

Subaxial cervical spine injury is essentially classified by mechanism of injury and degree of stability [1]. In addition to elucidating the mechanism of injury, it is equally important to be aware of the degree of stability of the lesion. Understanding of stability is a key factor for both the initial and the surgical treatment of patients to avoid worsening their neurological deterioration. Spinal cord injury (SCI) should be treated while considering these points. However, there has been a debate over the treatment of patients with SCI because of a lack of guidelines. In fact, various treatments from conservative management to radical operation are recommended for each pattern of injury.

With the advent of spinal instrumentation, patients with SCI can obtain a strong internal fixation without necessity of a halo brace, and start rehabilitation sooner and more smoothly. In contrast, conservative management with prolonged bed resting or with a halo brace may cause delay of rehabilitation as well as secondary cardiopulmonary deterioration. Thus, the authors recommend surgical intervention using spinal instrumentation in cases of instability or severe cord compression due to traumatic intervertebral disc extrusion or bone fragments.

In this paper, we describe our experience regarding surgical treatment for subaxial SCI, with special emphasis on surgical tactics using spinal instrumentation.

2 Patients and Methods

Between 1994 and 2005, 69 patients with SCI were surgically treated. They consisted of 53 males and 16 females, with age ranging from 16 to 84 years. There were 25 fractures or dislocations, while 44 cases were SCI without radiological abnormalities. Diagnosis was made with plain radiographs and CT. MRI was used for evaluation of the spinal cord as well as injury of the spinal column and paravertebral soft tissues. Myelography was not performed in any of the cases. The neurological status on admission was Frankel A or B in 19 cases and Frankel C or D in 50 cases. Preoperative skull traction was performed in cases with instability. Twenty-five patients with bony damage causing instability underwent emergency operations essentially within 48 h. Anterior arthoridesis was performed in 18 cases, while posterior arthrodesis was performed in 5 cases. Combined arthrodesis was performed in 2 cases with severe bony damage. Forty-four patients without radiological abnormalities underwent delayed operation. Mean follow-up period was 14.1 months.

3 Results

Plain radiography in flexion-extension study was most useful to understand instability. CT clearly delineated fractures or dislocations, while MRI well demonstrated cord compression, cord displacement or soft tissue injury. Eight patients in Frankel A or B (38%) showed grade 1 or 2 neurological recovery after an operation, although 4 died of respiratory disturbance within 6 months. There was no surgery-related neurological deterioration in Frankel C or D. No serious intraoperative complications occurred.

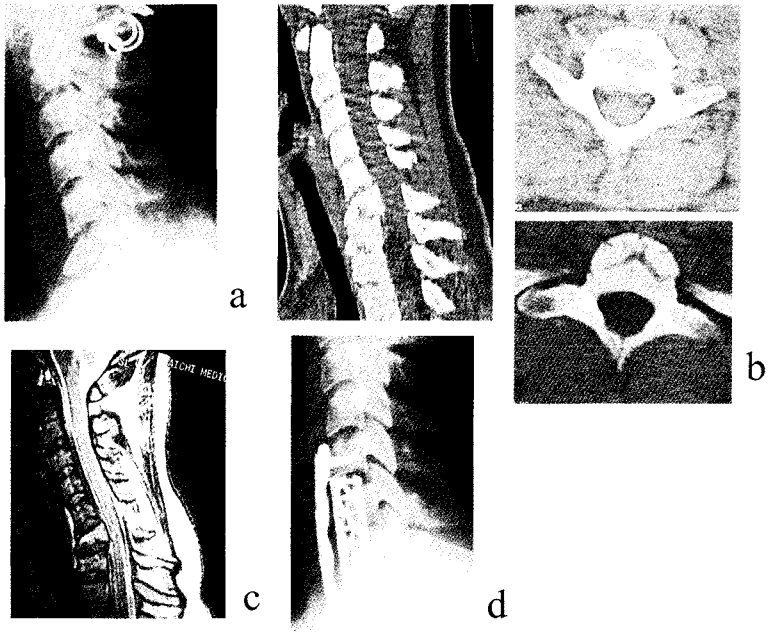


FIG. 1. **a** Plain lateral radiography revealing C6 and C7 burst fracture with anterior angulation. **b** CT confirming burst fracture of C6 and C7. **c** MRI demonstrating cord compression without intramedullary high signal intensity from C6–7 due to fractured vertebral body of C6 and C7. **d** Postoperative cervical radiography revealing correction of cervical alignment after arthrodesis using titanium mesh cage and a plate between C5 and T1

There were 2 hardware failures including dislodgement of a lateral mass plate and loosening of a screw of an anterior plate postoperatively.

4 Illustrative Cases

4.1 Case 1

This 22-year-old female met with a traffic accident, and arrived at our hospital by ambulance. Neurologically she was intact, although she complained severe neck pain. Radiological examination revealed burst fracture at C6 and C7 causing mild anterior angulation. The patient underwent anterior arthrodesis with interbody cage packed with bone chips and anterior plate between C5 and T1. The patient wore a SOMI brace for 1 month postoperatively (Fig. 1).

4.2 Case 2

This 55-year-old male became quadriplegic immediately after a motor vehicle accident. The patient's status was Frankel A. Radiological examination revealed bilateral interfacetal locking at C5–6. Skull traction nearly normalized cervical alignment, and

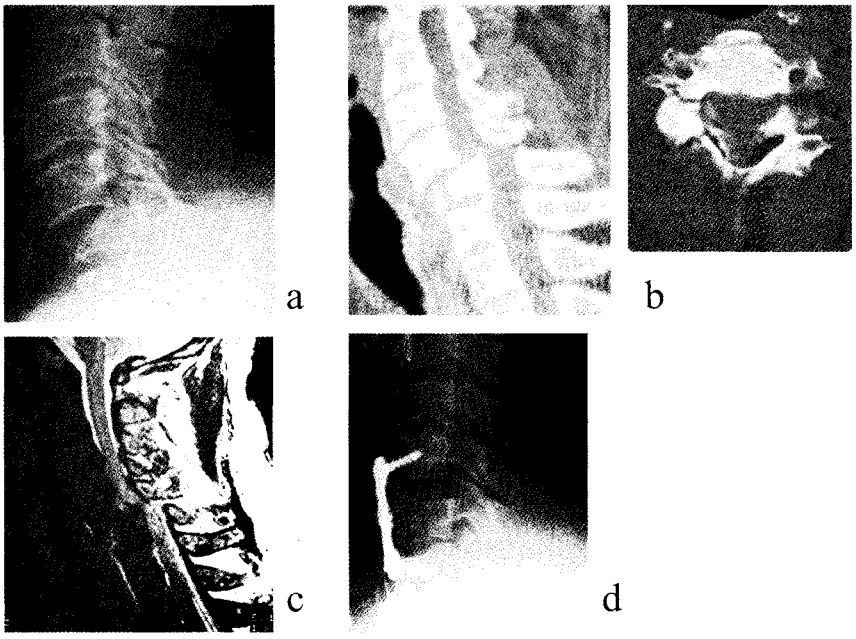


FIG. 2. **a** Plain lateral radiography revealing malalignment of the cervical spine at C5–6. **b** CT confirming bilateral interfacetal locking at C5–6. **c** MRI disclosing severe cord compression with swelling of the cord as well as intramedullary high signal intensity. **d** Postoperative cervical radiography disclosing restoration of the normal alignment of the cervical spine with iliac graft and a plate after reduction

then anterior arthrodesis using iliac graft and anterior plate was performed. Postoperatively the patient's neurological condition did not improve. The patient died of respiratory insufficiency 1 month after the accident (Fig. 2).

4.3 Case 3

This 47-year-old female was treated with a *cervical collar* for 3 months after she met with a traffic accident. The initial cervical plain radiograph revealed mild anterior angulation. The patient started to have neck pain 2 months after she stopped wearing a *cervical collar.* Repeated cervical radiography revealed aggravation of cervical alignment, and CT demonstrated unilateral interfacetal locking at C5–6. The patient underwent combined arthrodesis, because manual reduction failed. The patient's postoperative course was uneventful (Fig. 3).

5 Discussion

Management of cervical spinal cord injury is still controversial. Non-operative treatments have been supported by some experts [2–4], while operative treatments have been recommended by others [5–7]. Non-operative treatment essentially consists of

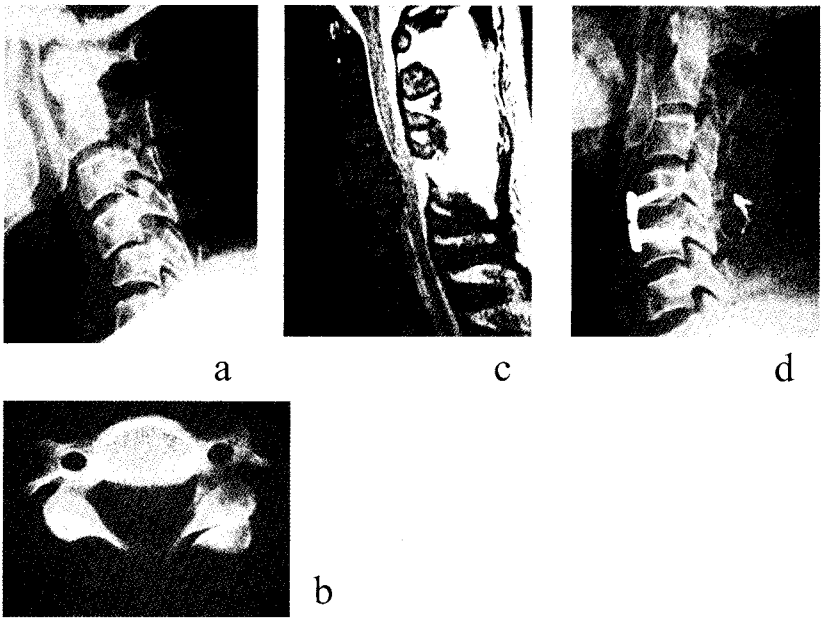


FIG. 3. **a** Plain cervical lateral radiography after conservative treatment with a *cervical collar* for 6 months revealing progression of anterior angulation. **b** CT confirming unilateral interfacetal locking at C5–6. **c** MRI revealing cord compression due to dislocated vertebral body. **d** Postoperative cervical radiography demonstrating restoration of the original cervical alignment after combined arthrodesis

mediation, bed resting, skull traction and an external orthosis. These conservative methods frequently force the patients to immobilize, and as a result, delay rehabilitation or procedure secondary cardiovascular or respiratory distress. Moreover, prolonged instability due to incomplete healing of the injured ligaments may occur. The failure rate of immobilization with skull traction and subsequent halo brace varies from 6 to 40% [2,6,8]. There was a case of delayed symptomatic kyphotic deformity after a *cervical collar* in our series. Furthermore, displacement of the intervertebral disc into the spinal column can occur during closed reduction and may increase the degree of neurological deficits derived from spinal instability. Thus, the authors consider operative treatment to be superior to non-operative treatment.

The types of operative approach that should be used remain controversial. The anterior and posterior cervical fusion procedures are successful for achieving spinal stability for patients with SCI. The anterior procedure may be recommended because of the advantages of removing a traumatic intervertebral herniated disc that compresses the spinal cord. To avoid delayed anterior angulation, anterior fixation using a bone graft and plate provides satisfactory results without dislodgement of the graft [9]. Posterior cervical fusion with wiring only shows a fairly high rate of postoperative kyphosis in SCI associated with facet dislocations [10,11]. On the other hand, stable fusion by the posterior procedure either with wiring and a plate or screws can

be achieved. [10]. Short segment and strong internal fixation using spinal instrumentation should be selected as a less invasive procedure in SCI with instability.

Fractures and dislocations, degree of instability and pathology of the spinal cord were diagnosed by cervical radiographs, CT and MRI. Although myelography and subsequent CTM are an established diagnostic technique, information obtained by this technique is not considered appreciable.

There were 4 Frankel A or B patients who died of respiratory disturbance. Postoperative MRI of these patients revealed progression of the intramedullary high signal intensity associated with spinal cord swelling after decompression and correction of cervical alignment. Initial impact on the spinal cord was considered fatal with no relation to the operative procedures in these cases.

References

1. Harris JH (1978) The radiology of acute cervical spine trauma. Williams and Wilkins, Baltimore
2. Bedbrook GM (1979) Spinal injuries with tetraplegia and paraplegia. J Bone Joint Surg 61B: 267–284
3. Donovan WH, Kopaniky D, Stolamann E, et al (1987) The neurological and skeletal outcome in patients with closed cervical spinal cord injury. J Neurosurg 66:690–694
4. Lind B, Sihlbom H, Nordwall A (1988) Halo-vest treatment unstable traumatic cervical spine injuries. Spine 13:425–432
5. Allen BL, Ferguson RL, Lejmann TR, et al (1982) A mechanic classification of closed, indirect fractures and dislocations of the lower cervical spine. Spine 7:1–27
6. Bucholz RD, Cheung KC (1989) Halo vest versus spinal fusion for cervical injury: evidence from an outcome study. J Neurosurg 70:884–892
7. O'Brien PJ, Schweigel JF, Thompson WJ (1982) Dislocations of the lower cervical spine. J Trauma 22:710–714
8. Dorr LD, Harvey JP, Nickel VL (1982) Clinical review of the early stability of spine injuries. Spine 7:545–550
9. Shapiro SA, Synder W, Kaufman K, et al (1999) Outcome of 51 cases of unilateral locked cervical facets: Interspinous braided cable for lateral mass plate fusion compared with interspinous wire and facet wiring with iliac crest. J Neurosurg 91 (Suppl. 1):19–24
10. Fehling MG, Cooper PR, Errico TJ (1994) Posterior plates in the management of cervical instability: Long-term results in 44 patients. J Neurosurg 81:341–349
11. Lukhele M (1994) Fractures of the vertebral lamina associated with unifacet and bifacet cervical spine dislocations. S Afr J Surg 32:112–114

Efficacy of Lateral Position on Minimally Invasive Cervical Expansive Open-Door Laminoplasty

Masaaki Nakajima, Masanori Chikama, and Masahiro Tsuboi

Summary. Spinal surgery for obese and elderly patients are dramatically increasing associated with the age of plenty and aging population. Minimally invasive surgery for those patients should be started with anesthesia and positioning. We report the efficacy of lateral position on cervical laminoplasty in minimally invasive fashion. We treated 15 patients with cervical myelopathy. The upper side of lateral position corresponds with the open-door side. If the patients have lung disease, good lung is kept down due to improved oxygen uptake. Patient neck is fixed in neutral alignment with straight axis of head-cervical-thoracic spine. Skin incision was 2 to 3 fingers breadth of 30 to 40 mm. Open-door laminoplasty was basically performed from C3 to C6 using hydroxyapatite spacer, and the lamina of C2 and C7 was undermined by drilling. Average Japanese Orthopedic Association (JOA) score improved from 8.3 pre-op to 14.7 post-op with improvement rate of 73.1%. No procedure-related complication was observed. Sputum of patients with chronic obstructive lung disease was safely aspirated by fiberscope on lateral position. The procedure was safely performed especially for the obese patients without increase of intraabdominal pressure, leading to less cardiopulmonary complication and less bleeding during surgery. Lateral position for cervical laminoplasty has the advantage of minimally invasive not only for the patients but also for anesthesiologist and neurosurgeon.

Key words. minimally invasive, cervical spine, expansive open-door, laminoplasty, lateral position

1 Introduction

Minimally invasive spinal surgery should be started with anesthesia and positioning. Surgeon must consider the positioning of a patient according to the varying degree between adequate accessibility to the surgical lesion and tolerance of the patient in

Okayama Saiseikai General Hospital, Department of Neurosurgery, 1-17-18 Ifukucho, Okayama 700-8511, Japan

the presence of the physiologic impairments produced by disease, age, obesity and the effects of anesthesia. Preoperative complications in respiratory system and cardiovascular system are increasing especially for aged patients. So proper positioning of a patient on an operating table should offer minimal interference with ventilation and circulation. Lateral position could be an alternative to prone position in posterior cervical spine surgery.

Expansive open-door laminoplasty, originally developed by Hirabayashi [1], has been widely used to treat ossification of the posterior longitudinal ligament (OPLL) and cervical spondylotic myelopathy. This procedure is efficacious for multilevel disease without the need for intersegmental fusion and provide no risk of pseudarthrodesis and less risk of adjacent segment degeneration compared with anterior surgery.

However, disadvantages of laminoplasty are postoperative axial neck and shoulder pain [2] and kyphosis. These factors still offer the hesitation for surgeon to adopt the posterior surgery. So technical improvement to reduce these problems is mandatory. We have performed Kihara's method (K-method) of minimally invasive cervical expansive open-door laminoplasty [3]. This procedure offers just 3 to 4 cm skin incision with minimal dissection of muscle and ligaments attached to the spine, and the exposure can be widely obtained from C2 to C7.

In this study, we report the efficacy of lateral position on minimally invasive cervical expansive open-door laminoplasty in terms of the combination of less invasive positioning and surgical technique.

2 Materials and Methods

Fifteen patients treated by K-method of expansive open-door laminoplasty [3] at the Department of Neurosurgery, Okayama Saiseikai General Hospital were retrospectively reviewed. There were 8 men and 7 women, whose mean age at the time of surgery was 65.6 years (range 50–78 years). The mean follow-up period was 12 months (range 2–34 months). All patients presented with symptoms and imaging studies of X ray, CT and MRI showed consistency with myelopathy. Diagnosis was multi-level cervical spondylosis in 12 patients, OPLL in 2 patients and soft disc hernia in one patient. High risk past history for general anesthesia and prone positioning were chronic obstructive pulmonary disease in one patient classified as Hugh-Johnes grade 3 and huge obesity in one patient, respectively.

Indications for surgery were patients with myelopathy refractory to conservative medical treatment. Patients with traumatic spinal cord injury, kyphosis and instability were excluded.

Patient with 3-pin skull fixation frame was fixed in the lateral decubitus position with head-up at 20 to 30 degrees and maintained straight axis of head-cervical-thoracic spine (Fig. 1). The neck was kept at neutral alignment to avoid spinal cord and muscle injury during the operation. Up-side of the body was the same side of open-door lamina. So the side of hydroxyapatite (HA) implants (Pentax Corp., Tokyo, Japan) originally designed by Kihara [3] always positions in the up-side of the neck in the lateral position. This makes the epidural bleeding drops downward and less blood pooling on the field of procedure. In case of the patient with chronic obstruc-

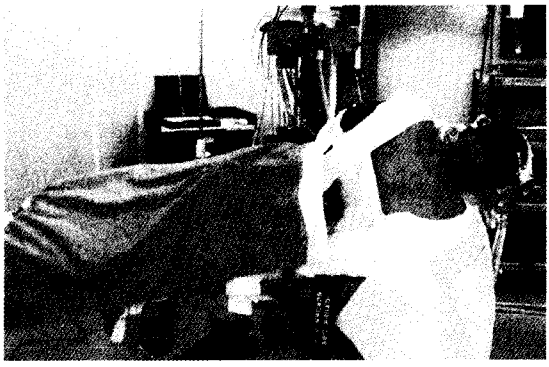


FIG. 1. Lateral position of a 65-year-old man. The neck is kept in neutral alignment with straight axis of head-cervical-thoracic spine

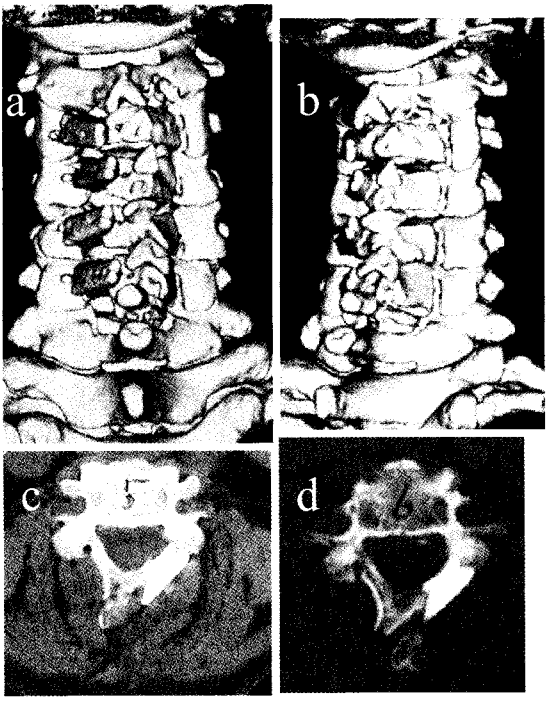


FIG. 2. Representative postoperative computer tomography (CT) scans obtained 3 months after surgery in a 65-year-old man. **a,b** Three dimensional bone CT showing fine fixation of hydroxyapatite (HA) implants from C3 to C6. **c,d** CT scan at C5 and C6, respectively, demonstrating fusion of HA spacers with the lamina and lateral mass

tive lung disease, good lung is kept down-side for improved oxygen uptake. Surgeon was able to sit and operate in a relaxed manner.

Procedure for K-method starts from the midline skin incision of 3 to 4 cm from the supposed C3 to C6 on the surface. The dissection is made along the nuchal ligament down to the lateral portion of the spinous process (SP) of C3 to C6. Following subperiosteal dissection of ipsilateral SP, lamina and medial facet, the base of SP from C3

to C6 was cut by oscillating-saw and contralateral lamina was exposed to medial facet. Then bilateral exposure from C3 to C6 was obtained with preservation of the interspinous and supraspinous ligaments. Lateral gutter at the lamina-facet junction was drilled from C3 to C6 on the hinge side on which corresponded with the down-side of the positioning, and then laminar door was made by drilling for open-door from C3 to C6. The lamina of C2 and C7 was undermined by drilling for canal decompression with preservation of ligamentous attachment to the SP to avoid postoperative axial pain and kyphotic deformity. After completion of C2-7 canal decompression, HA spacers were inserted from C3 to C6 to support the open-door construct and sutured tightly. No foraminotomies were performed. Patients began to walk in a soft collar on the next day postoperatively. The soft collar was maintained for a week and the patients discharged the hospital in 7 to 10 days after surgery.

The severity of myelopathy was evaluated by the Japanese Orthopaedic Association (JOA) scoring system for cervical myelopathy [3,4]. To assess the symptomatic recovery after surgery, the recovery rate proposed by Hirabayashi was used: recovery rate (%) = (postoperative JOA score—preoperative JOA score)/(17—preoperative JOA score) × 100. The incidence of axial neck pain and C5 palsy after surgery was assessed.

3 Results

Mean blood loss was 56.6 cc (range 0–200 cc). The mean preoperative JOA score was 8.3. The mean postoperative JOA score at discharge was increased to 14.7. The average recovery rate was 73.1%. No recurrences and progression of kyphosis were observed during follow-up period. C5 palsy occurred in one patient (6.6%) but was recovered in a few weeks. Axial neck pain occurred in one patient (6.6%) but was recovered in a few months. We had stopped the dissection of ligaments and muscles attached to C7 spinous processes, thereafter axial pain has not occurred. No procedure-related and perioperative complications were observed. Sputum of patients with chronic obstructive lung disease was safely aspirated by fiberscope on lateral position. HA implants were firmly fixed between lamina and lateral mass with fusion on CT scan (Fig. 2).

4 Discussion

Minimally invasive spinal surgery should include not only the operative technique but also anesthesia and proper patient positioning. Proper patient positioning for posterior cervical spine surgery should be designed to relieve the pressure to cervical paravertebral venous plexus, leading to the decrease of venous blood into the spinal canal. So neutral cervical alignment and lateral position during surgery contribute to less pressure on internal jugular vein and inferior vena cava, respectively.

Prone position offers several threats to circulation [5]. Especially for obese patient, intra-abdominal pressure could rise in the prone position in which might cause the decrease of venous return from the lower extremities unless the abdomen is relatively free from the surface of the operating table, leading to the inadequate cardiac output and hypotension. Lateral position for cervical laminoplasty could be an alternative to conventional prone position.

K-method of expansive open-door laminoplasty was considered as quite minimally invasive technique among many laminoplasty procedures in two reasons in this study. First, the recovery rate was 73.1% in this study compared with 20 to 81% reported in the literature [6]. Kihara have reported maximal recovery rate of 80.4% by K-method [3]. Second, axial neck pain after surgery was 6.6% in this study compared with 60 to 80% reported in the literature [2]. Kihara have reported incidence of neck pain and/or stiffness after surgery was 10%, and that no patients had disturbed activities of daily living 1 year after surgery [3]. Low incidence of axial pain might be attributable to the small skin incision and minimal dissection of posterior cervical supporting elements with complete preservation of ligaments and muscles especially attached to C2 and C7 spinous process.

5 Conclusion

This study demonstrated the combination of lateral positioning and K-method of laminoplasty would lead to minimally invasive surgery in total.

References

1. Hirabayashi K (1978) Expansive open-door laminoplasty for cervical spondylotic myelopathy (in Japanese). *Jpn J Surg* 32:1159–1163
2. Hosono N, Yonenobu K, Ono K (1996) Neck and shoulder pain after laminoplasty. *Spine* 21:1969–1973
3. Kihara S, Umebayashi T, Hoshimaru M (2005) Technical improvement and results of open-door expansive laminoplasty with hydroxyapatite implants for cervical myelopathy. *Neurosurgery* 57:ONS-1-ONS-8
4. Ogawa Y, Toyama Y, Chiba K, et al (2004) Long-term results of expansive open-door laminoplasty for ossification of the posterior longitudinal ligament of the cervical spine. *J Neurosurg (Spine 1)* 2:168–174
5. Martin JT (1993) The physiology of patient posture. Principles of anesthesiology. LEA&FEBIGER, Philadelphia, pp 163–173
6. Ratliff JK, Cooper PR (2003) Cervical laminoplasty: A critical review. *J Neurosurg* 98 (Suppl. 3):230–238

MR Tractography for Minimally Invasive Neurosurgery

Kei Yamada, Osamu Kizu, and Tsunehiko Nishimura

Summary. Diffusion tensor imaging (DTI) based tractography to elucidate the course of pyramidal and sensory tracts have recently become feasible for routine clinical practice. A typical imaging time for DTI in our institute is usually within ten minutes and postprocessing of the acquired data to generate preliminary results necessary for presurgical planning takes only 15 to 20 min. This brief review will describe the DTI methodology, optimization of the image quality and data post-processing, and utilization of the data for patient care.

Key words. MRI, diffusion-tensor imaging, diffusion-weighted image, tractography, brain tumor

1 Introduction

Surgical resection of brain tumors involving the so-called eloquent areas remains challenging, and various adjunct strategies have been employed to improve patient outcomes, including awake surgery, intraoperative navigation systems, and intraoperative electrical and chronic intracranial electrical stimulation. It has been also suggested that preservation of cortical as well as subcortical function is critical for improved outcomes. With the advent of magnetic resonance (MR) imaging, it is now possible to visualize the white matter fibers of the brain with diffusion tensor images (DTI), a technique also known as fiber-tracking or tractography [1–5].

Water-diffusion anisotropy (directionality) in the white matter of brain is defined on the basis of axonal alignment [6]. Water diffusion preferentially diffuses in a direction parallel to the axon's longitudinal axis but is relatively restricted in the perpendicular axis. This phenomenon can be represented mathematically by the so called

Department of Radiology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kajii-cyo, Kawaramachi Hirokoji Sagaru, Kamigyo-ku, Kyoto, Kyoto 602-8566, Japan

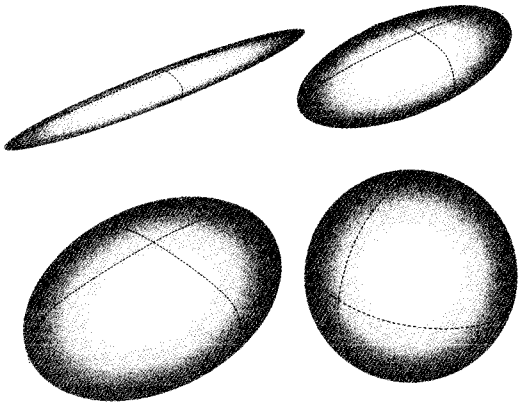


FIG. 1. Diffusion ellipsoids (tensors). When there is no directionality, the fractional anisotropy (FA) is zero (spherical). A typical tensor of a white matter bundle will have a cigar shape. When there are crossing fibers, the ellipsoid becomes flattened, resulting in "pancake" tensors (lower left)

diffusion ellipsoid, or tensor (Fig. 1). These tensors can be reconstructed to track three-dimensional macroscopic fiber orientation in the brain, and this technique is the only currently available method of characterizing the neuronal pathways in the living human brain. The present review will describe the basic technique as well as its application to presurgical planning for neurosurgical procedures.

2 Diffusion Tensor Imaging

2.1 Obtaining Images

DTI requires an MR unit with echo-planar imaging (EPI) capabilities, which is already available for most of the modern clinical MR scanners. Further, use of a parallel imaging technique is helpful to reduce image distortion [7]. A magnet with higher field strength (e.g. 3 Tesla magnets) would result in higher quality images within a shorter scan time. All the images in our institute are obtained using a whole body 1.5-T MR system (Gyroscan Intera; Philips Medical Systems, Best, The Netherlands) with parallel imaging capability.

2.2 Imaging Time

When the DTI-based tractography technique was first introduced, the major drawback was the duration of the examination (typically more than 30 min) [2] that was required to optimize the signal to noise ratio (SNR). In most cases, this long scan time is not clinically practical, as multiple series of studies may be required (e.g. multiple directions, MR angiography and venography), and patients with brain tumors may not be able to tolerate such lengthy examinations.

However, studies have demonstrated that fair tractographic results can be achieved with a DTI scanning of less than 5 min, particularly when sensorimotor tracts are the target [5]. While the resulting images may be relatively crude, they still provide valuable clinical information. In fact, DTI in our institute is typically performed at the end of the routine preoperative MR evaluation for brain tumors, rather than as a separate

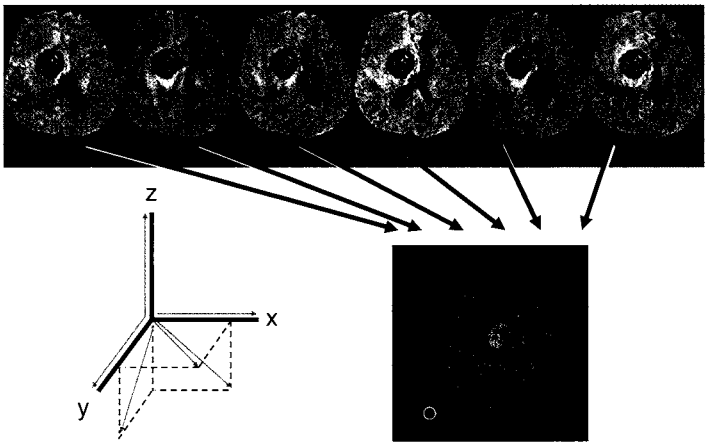


FIG. 2. DTI is calculated from at least six different source images with motion probing gradients (MPG) in different directions. Green arrows at the lower left corner indicate the MPG used in our imaging sequence when six directional scans are applied. Vector elements (lower right) are assigned to red (x element, left to right), green (y element, anteroposterior), and blue (z element, superoinferior) [Makris, Pajevic]. The intensities of the color map are scaled in proportion to the fractional anisotropy (FA)

test. To further optimize the SNR, our group is recently combining the results from several separate DTI examinations, each approximately 4 min in length, to gain final DTI images with a high SNR.

2.3 Imaging Sequence

DTI requires a minimum of six non-collinear motion-probing gradients (MPG) (Fig. 2). Our group, like most investigators, uses a single-shot EPI with a spin-echo Stejskal-Tanner sequence (repetition time ms/echo time ms; 6,000/88, and flip angle of 90°) with fifteen (or 32) motion-probing gradient orientations. A higher b-value is ideal but must be balanced against the SNR. Most investigators use a b-value of 800–1,200 s/mm^2.

A parallel imaging technique can reduce image distortion [8–10]. Our group uses a reduction factor of 2 or 3 for parallel imaging, thereby allowing image reconstruction with half or one-third of the encoding steps, respectively.

2.4 Image Quality

Several variables should be optimized to assure that images are of sufficient quality to perform reliable and reproducible fiber-tracking. First, the signal to noise ratio (SNR) of the images should be sufficiently high. Second, the image distortion should be minimized via use of parallel imaging techniques. Third, the images should be of relatively high resolution, especially in the z-axis, to promote a more isotropic form of the pixel shape. Fourth, the MPG angle should be as high as possible [11]. Our

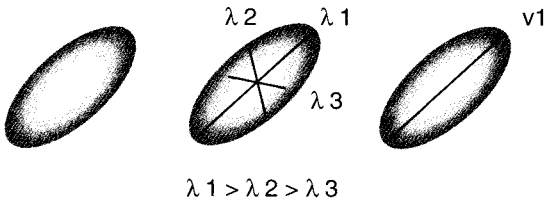


FIG. 3. The average fiber directions in the voxel are displayed by an ellipsoid. A three-dimensional axonal projection can be tracked by placing a seed point. Further detail of the technique can be found elsewhere [1]

group uses 15 directions for routine scanning and 32 directions for some presurgical cases.

Reduction of image distortion is a great challenge. Image distortion in diffusion-tensor MR images arises from magnetic field heterogeneity and large motion-probing gradients. Image distortion at the skull base and posterior fossa can be especially problematic in a conventional echo-planar MR imaging sequence. These artifacts may affect images of the brainstem, a critical location for placement of the seed points. Multishot echo-planar MR imaging can be used to reduce image distortion but this must be performed with cardiac gating to avoid echo artifacts on images obtained during the systolic phase. Unfortunately, cardiac gating limits the number of echoes acquired and prolongs the imaging time. Therefore, our group uses the parallel imaging technique to avoid geometric distortion. However, some groups argue that cardiac gating is still necessary, as brain pulsation may introduce significant error at certain anatomical points [12].

2.5 Post-processing

Since there is currently no commercially available software for image post-processing that runs on operating console of MR unit, the process is usually performed on a separate computer. A few relatively well-designed systems can be found and these will allow fiber-tracking method to become part of routine clinical practice. At out institution, DTI data are transferred to an off-line workstation (Precision 530; Dell, Round Rock, Texas) for analysis using PRIDE software (PRIDE; Philips Research Integrated Development Environment). Images are realigned with an automated image registration program to correct for any motion artifacts or image distortion. Diffusion-tensor elements and anisotropy at each voxel are then calculated using multivariate least squares fitting weighted by signal-to-noise ratio [13–15]. Anisotropy maps are obtained by means of orientation-independent fractional anisotropy (FA) [16]. The so-called diffusion ellipsoid is characterized by diffusion constants ($\lambda 1$, $\lambda 2$, and $\lambda 3$) along the three orthogonal directions and the direction (vector) of the longest axis (v1) (Fig. 3). Color maps based on diffusion-tensor MR images are generated from v1 (Fig. 2).

2.6 How Does It Work?

Translation of v1 into neural trajectories is achieved by the FACT (Fiber Assignment by Continuous Tracking) post-processing algorithm [1,17] (Fig. 4). Neural connections are mapped by designating two arbitrary regions of interest (ROI) in three-dimensional space. Tracking is terminated (stop criteria) when a pixel with low

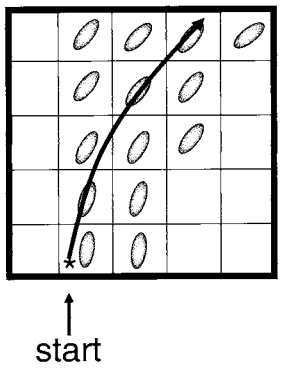
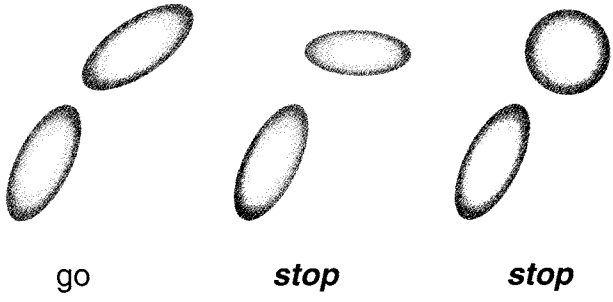


FIG. 4. The FACT program tracks the ellipsoids as long as the adjacent vectors are strongly aligned. When vector orientation becomes random, as judged quantitatively by the inner products of these vectors, the tracking is terminated. The program also terminates when the diffusion ellipsoids approach a spherical shape



fractional anisotropy or a predetermined trajectory curvature between two contiguous vectors is reached (Fig. 4). For presurgical depiction of sensorimotor tracts, at least two ROI are used. Fiber tracts that pass through both ROIs are used as the final tract of interest.

3 Clinical Application

3.1 Depicting Fiber Tracts

Various fiber tracts have been visualized using this technique. Most common target thus far is the pyramidal tract and this is probably due to the relative importance of this fiber bundle for activity in daily life. As discussed earlier, depiction of pyramidal tracts have been shown to be rather straightforward even with DTI data taken within 5 min. Depicting the sensory tracts, visual pathway, and other association fibers are somewhat more challenging.

Different tracts are depicted by placing ROI at various locations, which will base upon one's anatomical knowledge. Since there is no true "gold-standard" for tracto-

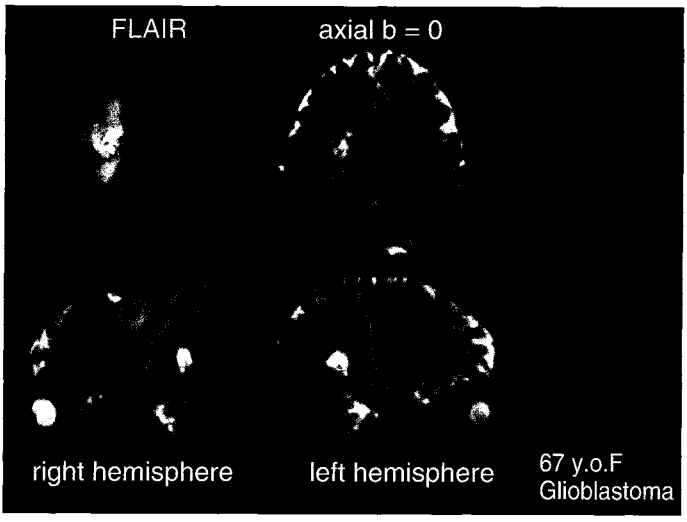


FIG. 5. A 67-year-old female patient underwent a presurgical evaluation for a brain tumor that was later diagnosed as glioblastoma multiforme. The pyramidal tract is indicated in purple, and the sensory tract is shown in green. There is posterior deviation in the pyramidal and sensory tracts due to mass effect from the lesion in the right frontal lobe. Note that the tracts running to or from the face/tongue areas are not well depicted; this is due to the "crossing-fiber" problem, which is addressed in Section 4

graphic results, the verification is done again by one's anatomical knowledge. This self-limiting nature of tractographic technique must be always kept in mind.

3.2 Pyramidal Tracts

Leaving the pyramidal tract intact during surgical procedure will be of primary interest to the neurosurgeon, and therefore, whether this tool is valid for pyramidal tract may be of vast importance. Fortunately, the tractography technique has been shown to be robust in this field and has been applied for neurosurgical planning [18–20]. Centrum semiovale would be one of the most difficult areas to obtain reliable landmark to identify the pyramidal tract and therefore this technique will be of remarkable help. There are some limitations for the technique and this will be discussed later in the final chapter. A typical case that may benefit from having tractography of pyramidal tract is illustrated in Fig. 5.

3.3 Sensory Tract

The sensory tract can be depicted by placing an ROI onto the primary sensory cortex and the dorsal part of brainstem. Aside from the differences in locations of the ROIs, the method is similar to that used for the pyramidal tract. However, the depicted sensory fibers tract are often less conspicuous than the pyramidal tract, possibly due to lower anisotropy in the sensory fibers than in the pyramidal tract.

3.4 Optic Radiation

When performing tractography of optic radiation tracts, our group utilizes ROIs placed in coronal planes at the occipital lobe and on the lateral geniculate body. However, ROI can be also placed in sagittal planes by identifying the optic radiation on color maps. One caveat is that the anterior parts of the Myer's loop tend to be underestimated, probably secondary to the presence of a crossing fiber from the medial geniculate body to the superior temporal gyrus (i.e. primary auditory cortex) [21]. Imaging results of the optic radiation also tend to be less robust than those of the pyramidal tract, probably because the typical shape of pixels of DTI are longer in the z-axis, since slice thickness are usually larger than the in-plane resolution. Whether a completely isotropic data set (e.g. $2 \times 2 \times 2$ mm) can improve the image quality should be addressed by future studies.

3.5 Clinical Applications other than Tumor Imaging

DTI can be applied to fields other than neuro-oncology. For examples, DTI has been used to characterize neuroanatomical changes due to stroke [22,23] and may be used to predict patient outcomes after stroke [24]. Further, DTI has been used to characterize arteriovenous malformation [25,26], amyotrophic lateral sclerosis (ALS) [27,28], pediatric ischemic brain insult [29,30], developmental CNS disease [31], multiple sclerosis [32], diffuse axonal injury (DAI) [33], and spinal cord lesions [34].

4 Limitation

4.1 Vasogenic Edema

A previous study reported that vasogenic edema is one of the most prominent factors that limits adequate imaging of brain tumors [5]. While it is conceivable that the presence of vasogenic edema can be to some extent compensated by using DTI scanning with higher SNR and higher b-values, this approach has not been fully successful in our experience. By contrast, use of different stop criteria (e.g. reduction of FA from 0.3 to 0.1–0.2) may be of benefit in improving image quality in the presence of vasogenic edema.

4.2 Spatial Resolution and SNR

Technical factors such as limited spatial resolution and low SNR of the acquired image will lead to poor quality of DTI and possibly to failure in tracking of fibers. Lin et al., who validated the accuracy of the principal eigenvector by comparing Mn^{2+}-enhanced optic tracts and DTI, reported that its accuracy depends on the SNR [35]. When considering the spatial resolution, one must bear in mind that it is not the in-plane resolution that is lacking. Slice thickness tends to be larger than the in-plane resolution for most of the MR imaging techniques. By reducing the slice thickness, one would gain spatial resolution in z-axis.

Our group uses a slice thickness of 3 mm without intersection gaps for routine presurgical evaluation. The field of view is 230 × 230 mm, and the image matrix is 128 × 128; thus, the size of a voxel is 1.8 × 1.8 × 3.0 mm. However, for some of the cases, we use a slice thickness of 2 mm, which results in near isotropic resolution (1.8 × 1.8 × 2.0 mm).

While achieving higher SNR results in improvement of image quality, it also requires a longer imaging time. However, patient considerations limit the imaging time, as discussed above, and, thus, also limit optimization of the SNR. Ultra-high field MR units may be of benefit in optimizing SNR without large increases in imaging time [36] but the penalty may be the higher degree of susceptibility artifact and resultant image distortion.

4.3 ROI Placement

Fiber-tracking is a user-defined process, and the results are dependent on the size and location of the seed ROIs [37]. In most cases, including ours, the selection of seed ROIs is based on anatomical landmarks. When tracking the fibers of patients harboring space-occupying brain lesions, it is desirable to choose ROI based on both anatomical and functional information. Therefore, an automated method or standard protocol for fiber-tracking is required to avoid bias. Furthermore, information obtained from functional evaluations such as fMRI and MEG may be able to facilitate a more objective post-processing protocol.

4.4 Crossing Fibers

Motor tracts of the brain should have a fan-shaped configuration at the level of the centrum semiovale. However, the fiber-tracking technique can only depict the fibers traveling to the vertex of the brain (Fig. 5). This is attributable to the existence of multiple crossing fibers at the level of the centrum semiovale which leads to inaccuracy in the estimation of the direction of anisotropy in these areas. The development of new models and methods seeks to provide solutions for these problems. Recent studies have shown successful reconstruction of multi-tensors and resolved multiple intravoxel fibers [38,39]. These new techniques may improve the reproducibility of fiber-tracking and solve the crossing fiber problem.

4.5 Validation

Perhaps most important limitation of the fiber-tracking technique is that it has not yet been fully validated and its true clinical efficacy remains to be confirmed, although attempts at validation using different strategies have been made [35,40,41]. Most of these efforts are based on comparisons of fiber-tracking images and known neuroanatomy. We evaluated tractography from a more functional perspective through a couple of cases who underwent intraoperative electrophysiological tests, which we believe will be another step toward the true validation of fiber-tracking technique [42]. We must keep in mind that this technique is still not complete in terms of fiber depiction and there is tend towards underestimation of the fiber tracts [42]. The tool has to be utilized with caution, knowing that we are only observing part of reality. By

fully accounting on the depict fiber tracts, one may damage eloquent fibers of the brain.

References

1. Mori S, Crain BJ, Chacko VP, et al (1999) Three-dimensional tracking of axonal projections in the brain by magnetic resonance imaging. *Ann Neurol* 45:265–269
2. Conturo TE, Lori NF, Cull TS, et al (1999) Tracking neuronal fiber pathways in the living human brain. Proc Natl Acad Sci U.S.A. 96:10422–10427
3. Gossl C, Fahrmeir L, Putz B, et al (2002) Fiber tracking from DTI using linear state space models: Detectability of the pyramidal tract. Neuroimage 16:378–388
4. Witwer BP, Moftakhar R, Hasan KM, et al (2002) Diffusion-tensor imaging of white matter tracts in patients with cerebral neoplasm. J Neurosurg 97:568–575
5. Yamada K, Kizu O, Mori S, et al (2003) Clinically feasible diffusion-tensor imaging for fiber tracking. Radiology 227:295–301
6. Wiegell MR, Larsson HB, Wedeen VJ (2000) Fiber crossing in human brain depicted with diffusion tensor MR imaging. Radiology 217:897–903
7. van den Brink JS, Watanabe Y, Kuhl CK, et al (2003) Implications of SENSE MR in routine clinical practice. Eur J Radiol 46:3–27
8. Golay X, Brown SJ, Itoh R, et al (2001) Time-resolved contrast-enhanced carotid MR angiography using sensitivity encoding (SENSE). AJNR Am J Neuroradiol 22:1615–1619
9. Golay X, Pruessmann KP, Weiger M, et al (2000) Presto sense: An ultrafast whole-brain fMRI technique. Magn Reson Med 43:779–786
10. Kyriakos WE, Panych LP, Kacher DF, et al (2000) Sensitivity profiles from an array of coilsfor encoding and reconstruction in parallel (SPACE RIP). Magn Reson Med 44:301–308
11. Jones DK (2003) Proceedings of the 11th annual meeting of ISMRM. Toronto, Canada, p 72
12. Jones DK (2005) Contribution of cardiac pulsation to variability of tractography results. proceedings of the 13th annual meeting of ISMRM. Miami, FL, p 222
13. Chenevert TL, Brunberg JA, Pipe JG (1990) Anisotropic diffusion in human white matter: Demonstration with MR technique in vivo. Radiology 177:401–405
14. Basser PJ, Mattiello J, LeBihan D (1994) MR diffusion tensor spectroscopy and imaging. Biophys J 66:259–267
15. Basser PJ, Mattiello J, LeBihan D (1994) Estimation of the effective self-diffusion tensor from the NMR spin echo. J Magn Reson B 103:247–254
16. Pierpaoli C, Basser PJ (1996) Toward a quantitative assessment of diffusion anisotropy. Magn Reson Med 36:893–906
17. Xue R, van Zijl PCM, Crain BJ, et al (1999) In vivo three-dimensional reconstruction of rat brain axonal projections by diffusion tensor imaging. Magn Reson Med 42:1123–1127
18. Coenen VA, Krings T, Mayfrank L, et al (2001) Three-dimensional visualization of the pyramidal tract in a neuronavigation system during brain tumor surgery: First experiences and technical note. Neurosurgery 49:86–93
19. Hendler T, Pianka P, Sigal M, et al (2003) Delineating gray and white matter involvement in brain lesions: Three-dimensional alignment of functional magnetic resonance and diffusion-tensor imaging. J Neurosurg 99:1018–1027
20. Holodny AI, Schwartz TH, Ollenschleger M, et al (2001) Tumor involvement of the corticospinal tract: Diffusion magnetic resonance tractography with intraoperative correlation. J Neurosurg 95:1082
21. Yamamoto T, Yamada K, Nishimura T, et al (2005) Tractography to depict three layers of visual field trajectories to the calcarine gyri. AJO (in press)

22. Kunimatsu A, Aoki S, Masutani Y, et al (2003) Three dimensional white matter tractography by diffusion tensor imaging in ischaemic stroke involving the corticospinal tract. *Neuroradiology* 45:532–535
23. Yamada K, Mori S, Nakamura H, et al (2003) Fiber-tracking method reveals sensorimotor pathway involvement in stroke patients. *Stroke* 34:E159–162
24. Konishi J, Yamada K, Kizu O, et al (2005) MR tractography for the evaluation of the functional recovery from lenticulostriate infarct. *Neurology* 64:108–113
25. Yamada K, Kizu O, Ito H, et al (2004) Tractography for an arteriovenous malformation. *Neurology* 62:669
26. Yamada K, Kizu O, Ito H, et al (2005) Tractography for arteriovenous malformations near the sensorimotor cortices. *AJNR Am J Neuroradiol* 26:598–602
27. Aoki S, Iwata NK, Masutani Y, et al (2005) Quantitative evaluation of the pyramidal tract segmented by diffusion tensor tractography: Feasibility study in patients with amyotrophic lateral sclerosis. *Radiat Med* 23:195–199
28. Abe O, Yamada H, Masutani Y, et al (2004) Amyotrophic lateral sclerosis: Diffusion tensor tractography and voxel-based analysis. *NMR Biomed* 17:411–416
29. Yoo SS, Park HJ, Soul JS, et al (2005) In vivo visualization of white matter fiber tracts of preterm- and term-infant brains with diffusion tensor magnetic resonance imaging. *Invest Radiol* 40:110–115
30. Hoon AH Jr, Lawrie WT Jr, Melhem ER, et al (2002) Diffusion tensor imaging of periventricular leukomalacia shows affected sensory cortex white matter pathways. *Neurology* 59:752–756
31. Lee SK, Kim DI, Kim J, et al (2005) Diffusion-tensor MR imaging and fiber tractography: A new method of describing aberrant fiber connections in developmental CNS anomalies. *Radiographics* 25:53–68
32. Pagani E, Filippi M, Rocca MA, et al (2005) A method for obtaining tract-specific diffusion tensor MRI measurements in the presence of disease: Application to patients with clinically isolated syndromes suggestive of multiple sclerosis. *Neuroimage* 26:258–265
33. Le TH, Mukherjee P, Henry RG, et al (2005) Diffusion tensor imaging with three-dimensional fiber tractography of traumatic axonal shearing injury: An imaging correlate for the posterior callosal "disconnection" syndrome: Case report. *Neurosurgery* 56:189
34. Tsuchiya K, Fujikawa A, Suzuki Y (2005) Diffusion tractography of the cervical spinal cord by using parallel imaging. *AJNR Am J Neuroradiol* 26:398–400
35. Lin CP, Tseng WY, Cheng HC, et al (2001) Validation of diffusion tensor magnetic resonance axonal fiber imaging with registered manganese-enhanced optic tracts. *Neuroimage* 14:1035–1047
36. Okada T, Miki Y, Yamamoto K, et al (2005) Integration of diffusion tensor tractography of the corticospinal tract using 3 T with intraoperative white matter stimulation mapping: A preliminary result to validate the corticospinal tract localization. Radiology (in press)
37. Clark CA, Barrick TR, Murphy MM, et al (2003) White matter fiber tracking in patients with space-occupying lesions of the brain: A new technique for neurosurgical planning? Neuroimage 20:1601–1608
38. Tuch DS, Reese TG, Wiegell MR, et al (2002) High angular resolution diffusion imaging reveals intravoxel white matter fiber heterogeneity. *Magn Reson Med* 48:577–582
39. Frank LR (2002) Characterization of anisotropy in high angular resolution diffusion-weighted MRI. *Magn Reson Med* 47:1083–1099
40. Ciccarelli O, Toosy AT, Parker GJ, et al (2003) Diffusion tractography based group mapping of major white-matter pathways in the human brain. Neuroimage 19:1545–1555
41. Parker GJ, Stephan KE, Barker GJ, et al (2002) Initial demonstration of in vivo tracing of axonal projections in the macaque brain and comparison with the human brain

using diffusion tensor imaging and fast marching tractography. Neuroimage 15:797–809

42. Kinoshita M, Yamada K, Hashimoto N, et al (2005) Fiber-tracking does not accurately estimate size of fiber bundle in pathological condition: Initial neurosurgical experience using neuronavigation and subcortical white matter stimulation. *Neuroimage* 25:424–429

Intraoperative MRI

Masayuki Matsuda[1], Akihiko Shiino[1], and Shigehiro Morikawa[2]

Summary. We use a vertically-oriented open MRI system, 0.5T SIGNA SP/i, during operation as one of the means of neuronavigation. The patient's head is placed between the two doughnut-shaped magnets, 58 cm apart from each other. The patient is brought in either through the gap between the two magnets or through the hole of the doughnut depending on the location of the lesion. Because of this limited working space only one or two neurosurgeons are allowed as the operator(s) depending on the direction the patient is brought in. During operation we monitor real time MR images on any planes directed by an optical tracking system as well as usual multi-slice MR images updated for brain shift. Real-time images on two perpendicular planes which show the needle path, and re-formatted images from reference volume data on the corresponding planes, are immediately shown on the monitor. The updated reference images with either T1- or T2-weighted sequence are much better in quality than the real time images. The combination of the real-time and re-formatted images on two perpendicular planes is quite helpful for intraoperative navigation. Sampling points can be marked and recorded on the 3-dimensional images for intraoperative as well as postoperative histological confirmation.

Key words. intraoperative MRI, neuronavigation, open MR

Various kinds of neuronavigation are now used to carry out precise, safe and less invasive neurosurgical procedures. We use a vertically-oriented open MRI system, 0.5T SIGNA SP/i (General Electric, Milwaukee, WI, U.S.A.) during operation as one of the means of neuronavigation. It looks like two doughnut rings are standing side by side, nicknamed "Double Doughnuts" (Fig. 1). The patient's head is placed between the two doughnut-shaped magnets, 58 cm apart from each other. Because of this limited working space only one or two neurosurgeons are allowed as the operator(s) depend-

[1] Department of Neurosurgery, [2] Biomedical MR Science Center, Shiga University of Medical Science, Tsukinowa Cho, Seta, Ohtsu, Shiga, Japan

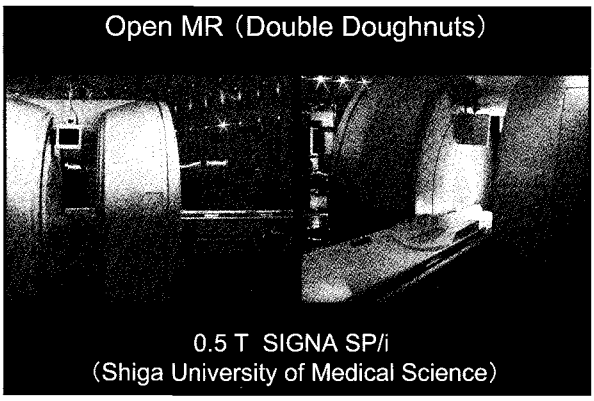


FIG. 1. Our intraoperative open MR system, 0.5T SIGNA SP/i. The vertical gap between the two magnet is 58 cm

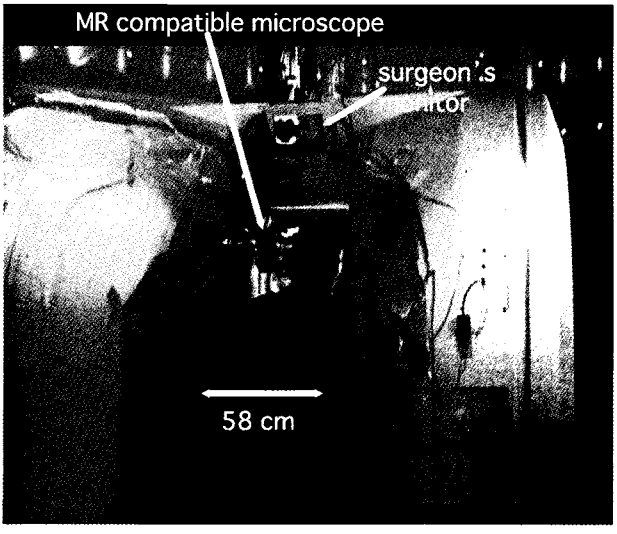


FIG. 2. Operation with side dock

ing on the direction the patient is brought in. This direction is decided by the location of the target lesion. For general surgery and spinal surgery the patient is placed through the magnet bore, what we call "front dock", and two surgeons can stand facing each other like in the usual operating theater. For neurosurgical procedure the patient is usually introduced from the side of the magnet, an open space between the two magnets, what we call "side dock". Only one neurosurgeon can work on the patient. As working space is very limited, the MR-compatible operating microscope (Studer Medical Engineering AG, Rheinfall, Switzerland) can be tilted about only 10 degrees to one side, 20 degrees at most from side to side (Fig. 2).

The real-time images are available on any planes and at any angles we need using an interactively operating optical tracking system (Fig. 3). The positions of three LEDs in the pointer, FlashPoint 5,000 (Image Guided Technologies, Boulder, CO, U.S.A.), are

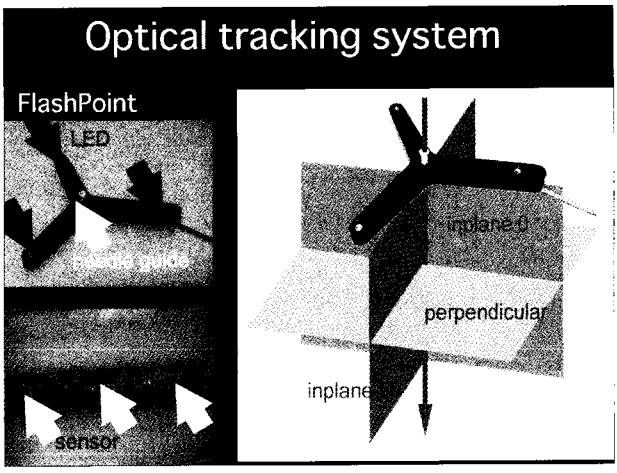


FIG. 3. Optical tracking system. FlashPoint has an LED at the end of the three arms (left upper, *black arrows*). A biopsy needle is introduced through the center hole (left upper, *white arrow*). Sensors which receive signal from the LEDs are installed in the ceiling of the magnet housing (left lower, *arrows*). MR images are obtainable on three planes; axial, coronal and sagittal, or on any three planes perpendicular each other (right)

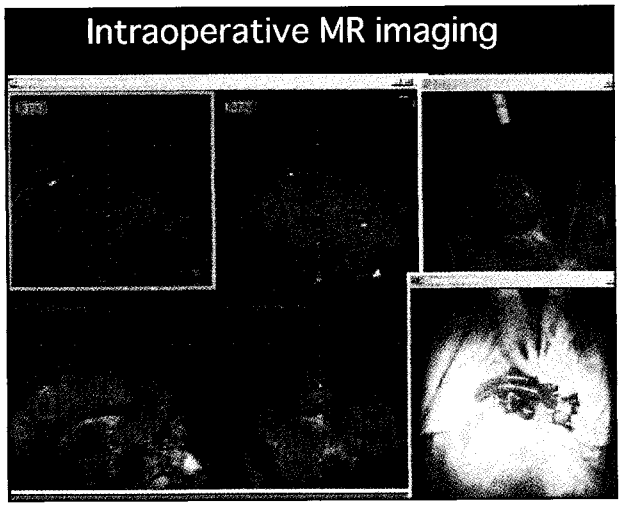


FIG. 4. Intraoperative MR image monitor. Real-time image with a biopsy needle is shown every two seconds alternately switching between the two planes perpendicular each other (upper left and center). Higher quality image reconstructed from the updated 3D volume data on the same plane as the real-time one is shown at the same time (lower left and center). Biopsy sites are marked on the 3D image (upper right). Monitor of operative field (lower right)

detected by the sensors placed in the ceiling of the magnet housing. A biopsy needle is introduced through the hole in the center of the FlashPoint. We can get the real-time images right on the plane of the needle perpendicular each other and the image perpendicular to the needle.

The real-time images usually taken every 2 s, however, are not always good in resolution and quality because of limited acquisition time. We have developed our own navigation software that enables us to monitor the higher quality MR images reconstructed from the reference 3-D volume data on the same planes as the real-time images. This software also has a capability to control the MR scanner. The images can be alternately switched between the two planes perpendicular each other. The reference 3-D volume data for reconstruction can be updated for brain shift at any time during operation with the acquisition time of 5 to 6 min. Combination of the updated reconstructed images with T1- or T2-weighted sequence and the real-time images are very helpful to decide where to biopsy or resect or to know where we are and the extent of tumor resection (Fig. 4).

Sampling sites on the wall of the cavity for intraoperative frozen section to confirm removal of the tumor or for postoperative histological examination are marked one by one and recorded on the 3-D images.

There are some drawbacks in this MR navigation system. In addition to requirement of expensive MR-compatible surgical instruments, the patient's position is subject to restriction due to the table which slides only in the horizontal direction, and the inclination of the lighting axis of the microscope is limited due to narrow working space. Therefore, the craniotomy sites are restricted. However, in spite of those drawbacks the intraoperative MR imaging is useful for precise, safe and less invasive procedures when patients are appropriately selected.

Clinical Significance of Positron Emission Tomography in Brain Tumor Surgery

KATSUYOSHI MINEURA

Summary. The author has clinically employed positron emission tomography (PET) in the choice of therapeutic modality including surgical indication and approach in the treatment of brain tumor. The uptake and distribution of ^{18}F-fluorodeoxyglucose (FDG) is important landmark for malignancy and tumor extent. The tumor portion including a peak FDG uptake portion is a target for accurate diagnosis of malignancy. High-grade gliomas show heterogeneous uptake patterns, reflecting a topographic variation of cellular composition consisting of aggregated tumor cells, necrosis, and peritumoral edema. Distortion of FDG uptake pattern in brain structure implies diffusely infiltrating growth of tumor into the surrounding tissue, thus limiting surgical resection. Among mostly benign tumors such as meningioma and central neurocytoma, atypical subsets have a relatively high uptake of FDG. The maximum reduction of tumor mass using pertinent approach, when atypical, may result in prolonging high levels of performance status and enhancing treatment efficacy of adjuvant therapy. Clinical use of PET provides more appropriate and less invasive treatment strategy based on the biologic characteristics of brain tumors and the function of surrounding brain structures.

Key words. positron emission tomography (PET), ^{18}F-fluorodeoxyglucose (FDG), surgical indication, surgical approach

1 Introduction

Surgical indication in the management of brain tumors is based on many clinical factors including clinical history, neurologic findings, neuroradiologic findings, and an evaluation of the benefits and risks throughout surgical management. The goal of brain tumor surgery is the removal of as much tumor as possible without causing new

Department of Neurosurgery, Kyoto Prefectural University of Medicine, Kawaramachi Hirokoji, Kamigyo-ku, Kyoto 602-8566, Japan

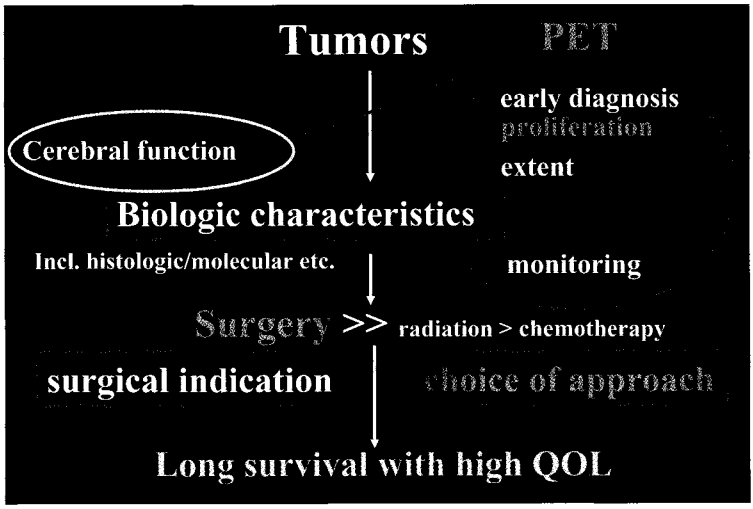


FIG. 1. Strategy for minimum invasive neurosurgery in brain tumors. PET provides functional data on the blood flow and metabolism of brain tumor as well as brain in *in vivo* manner. PET together with other biologic characterizations offers pertinent modes of treatments and increases quality of life in brain tumor patients

neurological deficit through appropriate approaches. Innovation of microsurgical technique and tools such as neuroendoscopy and neuronavigation system can overcome some difficulty in neurosurgical procedures and extend surgical application in brain tumor therapy. Further, common use of a variety of neuroimaging, functional mapping, and cranial nerve monitoring leads to more favorable surgical results (Fig. 1).

Current development in functional neuroimaging characterizes in vivo physiological and biochemical process of brain tumors as well as the surrounding brain. The unique property of positron emission tomography (PET) is the quantitative determination of blood flow and metabolism of brain tumors. Glucose metabolism as measured by ^{18}F-fluorodeoxyglucose (FDG)-PET is an accepted indicator of the malignancy of brain tumors. The author has clinically applied PET including FDG on the diagnosis and therapy monitoring in brain tumors. More than 600 of PET examinations have been done since 1983. Accumulated knowledge of relationship between PET findings and clinical factors has been introduced in the decision to surgical indication and the choice of surgical approach.

The present paper describes clinical significance of FDG-PET in brain tumor surgery of cerebral gliomas, central neurocytoma, and meningioma.

2 Cerebral Gliomas

Histologic analysis remains the most important factor in the prognosis of cerebral gliomas. Histologic confirmation is, however, a prerequisite for extirpation of a tumor at various degrees, ranging from biopsy to extensive resection. Diagnoses based on

the often limited sample of tumor tissue accessible to surgical techniques, are not always representative of the full malignancy of a tumor. Surgery, and especially a biopsy, can easily underestimate the degree of malignancy. Since PET can image the entire tumor, it overcomes such problems with histologic evaluation alone.

More than 60% of gliomas have a regional cerebral metabolic rate of glucose (rCMRGl calculated by FDG-PET) higher than that of the contralateral white matter, and approximately 40% have a higher rCMRGl value than that of the gray matter. Among high-grade gliomas, the histologic grade is less predictive, because the specimens do not always contain the most aggressive part of tumor [1].

High-grade gliomas show a heterogeneous pattern, whereas low-grade gliomas show a relatively homogeneous pattern of FDG uptake within each tumor. A peak activity is detected mostly at the periphery of the tumor. The pattern of tumor rCMRGl in high-grade reflects topographic variation of cellular composition consisting of aggregated tumor cells, necrosis, and perifocal edema (Fig 2) [2]. Areas with high rCMRGl represent metabolically active portions or tumor cell aggregations within tumors determined, in many cases, on the basis of both computed tomography (CT)/magnetic resonance (MR) imaging and autopsy findings. Preoperative recognition of active zones can determine the route for the adequate tumor tissues that will allow accurate prognosis and maximize therapeutic effectiveness.

^{11}C-methionine (Met) images clearly show the existence and localization of gliomas. Met images are more informative in mainly infiltrative glioma such as gliomatosis cerebri, where the anatomic methods of CT/MR imaging often fail to show significant abnormalities [3]. Thus, PET together with a variety of tracers can provide crucial qualitative and quantitative data on biologic and morphologic characteristics of gliomas [4].

3 Central Neurocytoma

Central neurocytoma occurs in young adults, is usually located in the lateral ventricle, and can proliferate within the ventricle. Better prognosis after more extensive resection is noted in most reports. However, some tumors contain histologically malignant features, and occasionally recur shortly after resection or they are disseminated and require further surgeries or adjuvant radiotherapy.

rCMRGl values of most central neurocytomas range between 30 and 70% of the rCMRGl values for the gray matter. These tumors show no recurrence or regrowth in the postoperative follow-up periods indicating that these tumors have a consistently low activity of proliferation. By contrast, tumors exhibit a relatively high rCMRGl value, which is almost equal to the value found in the gray matter (Fig. 3) [5]. This patient had been free of symptoms transiently after partial removal but had later presented with headaches; tumor progression was soon found on follow-up neuroimaging [6].

Transcortical and transcallosal approaches are commonly used for the surgery of central neurocytoma. Choice of approach depends on site, size, and extension of tumor. Maximum utilization of various direction of operative route within the limited operative site well identifies tumor as distinct from surrounding brain structures. To better visualize the interface between tumor and the surrounding tissue, the direction

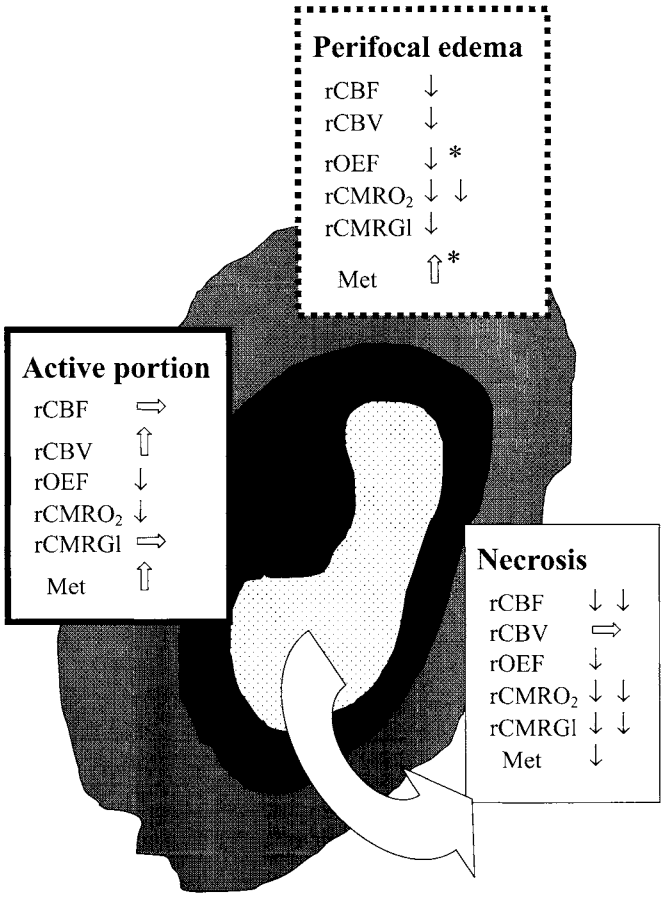


FIG. 2. Topographic pattern of cellular composition consisting of aggregated tumor cells (Active portion: solid area), necrosis (sparse dot area), and perifocal edema (dense dot area) in high-grade gliomas. Regional cerebral blood flow (rCBF), oxygen extraction fraction (rOEF), and the metabolic rate of oxygen ($rCMRO_2$) are obtained using $C^{15}O_2$ and $^{15}O_2$ according to the ^{15}O steady-state model. Regional cerebral blood volume (rCBV) is determined after inhalation of $C^{15}O$. rCMRGl images are scanned following an intravenous injection of FDG. The uptake of ^{11}C-methionine (Met) is analyzed after an intravenous injection of Met. (Modified from reference 2). ⇑, increase; ⇒, unchanged; ↓ and ↓↓, decrease as compared with parameters of the gray matter; *, dependent on invasiveness of tumor cells

of surgical approach is basically parallel to its long axis. Further, accurate estimation of tumor proliferating activity is an important consideration in determining the appropriate approach and the mode of tumor resection, and surgeons' attitudes for the surgical strategy of central neurocytomas.

The clinical benefits of adjuvant radiotherapy in the treatment of central neurocytoma remain unclear. Radiotherapy may play a beneficial role in improving the quality of life for patients who have persistent symptoms due to residual tumors. During post-

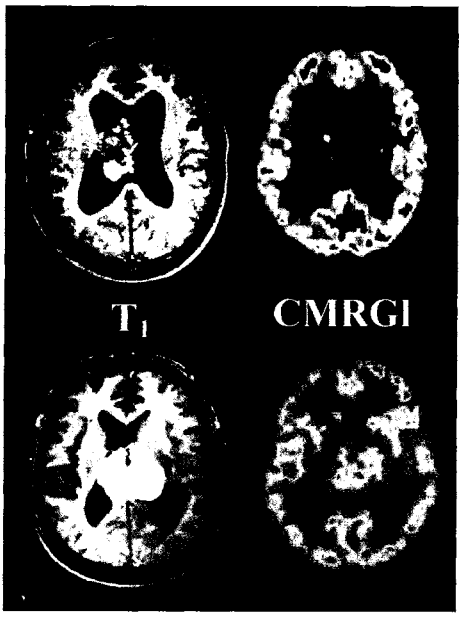


FIG. 3. Central neurocytoma. The tumor showing low uptake of FDG have no recurrence (Upper MR and PET), whereas the tumors exhibiting a relatively high rCMRGl value, almost equal to the value of gray matter have tumor progression shortly after partial removal (Lower MR and PET). (Cited from reference 5)

treatment follow-up periods, FDG-PET can assist in assessing residual tumors and the early detection of tumor recurrence.

4 Meningioma

Intracranial meningiomas are generally considered as benign tumors and are curable after surgical removal. However, there are subsets of atypical type meningiomas showing aggressive behavior and tumor recurrence.

Fig. 4 shows temporal base meningioma with FDG accumulation, indicating high proliferation rate of tumor. Therefore, the author aimed at eradiating the tumor as extensively as possible including the attached and adjacent dura matter. Knowledge of altered blood flow and metabolism in the surrounding brain suggests us gentle manipulation of both tumor and brain during surgical procedures. Ultrasonic surgical aspirator and laser are useful to vaporize tumor tissue with minimal mechanical and thermal damage to normal tissue. The transzygomatic approach was selected for this radical resection. PET findings to evaluate proliferation rate may also apply meningiomas at the other sites.

rCMRGl in meningiomas is correlated with tumor recurrence and tumor growth. Most PET studies concerning FDG have used the specified rate constants of normal brain tissue for calculating autoradiographic rCMRGl. The rate constants in tumor tissue varied widely dependently on tumor tissue components including tumor vessels and stroma. Interpretation of PET images is cautious in hypervascular meningiomas. Tumor images seem hot because of abundant tumor vessels. The determination of rCMRGl in hypervascular meningiomas necessitates kinetic rate constants and kinetic rCMRGl using dynamic PET [7,8].

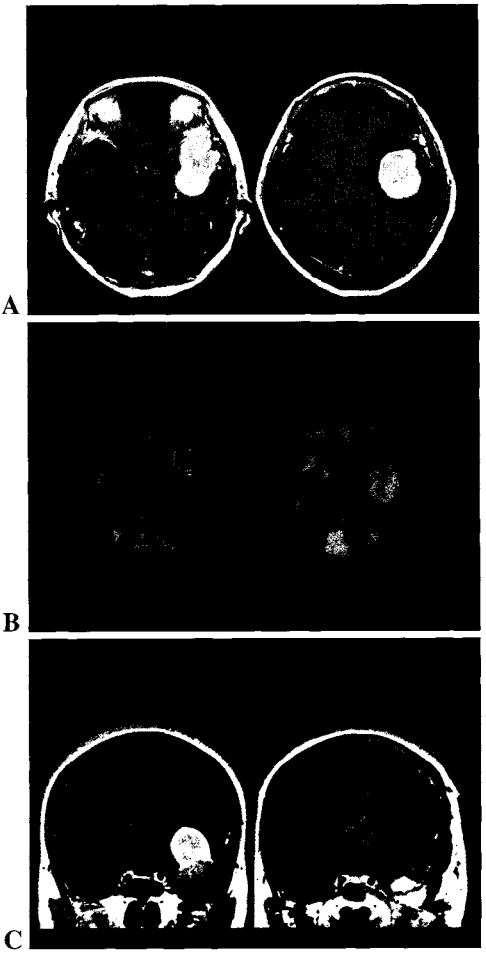


FIG. 4. Temporal base meningioma. **A** MR images a homogenously enhancing tumor at the temporal base. **B** FDG accumulates intensely in the lesion and less in the surrounding brain. **C** Dumbbell-shaped meningioma is extensively eradicated trough transzygomatic approach (left: preoperative, right: postoperative). Direction of surgical axis parallel to the long axis of tumor maximizes resection of tumor and minimizes mechanical pressure to the surrounding brain during surgery

5 Discussion

Among PET parameters, FDG has been most widely accepted as an informative positron tracer. Nowadays, anatomic images such as MR imaging may mostly diagnose type of brain tumors by its anatomic location and morphologic findings. A single FDG-PET study is not always sufficient for the differential diagnosis of brain tumors; however, PET adds importantly functional information to anatomic images. FDG tracers sometimes accumulate in the non-tumor lesions of brain abscesses and cerebral sarcoidosis. For differentiating these diseases, sequential FDG-PET studies as well as combined PET studies with blood flow and oxygen metabolism may provide a reliable alternative [9].

The rCMRGl value measured by PET represents the sum of rCMRGl per cell in brain tumors. The value strongly correlates with cellularity of tumors without necrosis,

microcysts, and hematoma. This correlation between rCMRGl and cellularity has also been noted in meningioma, as a representative, benign brain tumor usually having no necroses. In a lineage of astrocytoma and glioblastoma, even with necrosis, a peak activity within a tumor and a higher value reflects more proliferative areas and indicates a worse prognosis.

Central neurocytomas have a propensity towards low activities of glucose metabolism. Approximately 20% of central neurocytomas are subject to atypical subset, and maximum resection and close follow-ups are needed. FDG-PET has been powerful to differentiate atypical subset among central neurocytomas, and may indicate radiotherapy as an adjuvant treatment.

The increasing use of CT/MR imaging has led to an increased detection of asymptomatic brain tumors such as meningioma, but it is not clear how these lesions should be managed surgically. Therefore, FDG-PET as a proliferative index may become more important to evaluate the viability and aggressiveness of these asymptomatic brain tumors prior to surgery. Thus, PET studies together with a variety of tracers and multidisciplinary PET study can lead to high quality of brain tumor surgery and result in better prognosis in the treatment of brain tumors.

Acknowledgments. This work was supported in part by Grant-in-Aid No. 16390416 for Scientific Research from the Ministry of Education, Culture, Science, Sports, and Technology, Japan.

References

1. Mineura K, Sasajima T, Kowada M, et al (1994) Perfusion and metabolism in predicting the survival of patients with cerebral gliomas. Cancer 73:2386–2394
2. Mineura K, Sasajima H (2001) PET and SPECT. Clin Neurosci 19:301–304 (in Japanese)
3. Mineura K, Sasajima T, Kowada M, et al (1991) Innovative approach in the diagnosis of gliomatosis cerebri using carbon-11-L-methionine positron emission tomography. J Nucl Med 32:726–728
4. Takahashi Y, Imahori Y, Mineura K (2003) Prognostic and therapeutic indicator of fluoroboronophenylalanine positron emission tomography in patients with gliomas. Clin Cancer Res 9:5888–5895
5. Mineura K, Sasajima H, Tomura N (1999) SPECT·PET. In: Takaura K, Saitou I, Satoh K (eds) New Approach Series, vol 9, Brain tumors, Medical View, Tokyo, pp 58–65 (in Japanese)
6. Mineura K, Sasajima T, Itoh Y, et al (1995) Blood flow and metabolism of central neurocytoma. A positron emission tomography study. Cancer 76:1224–1232
7. Shioya H, Mineura K, Sasajima T, et al (1995) Tumor aggressiveness determined by kinetic analysis of glucose metabolism in meningiomas. Neuroradiology 37 (Suppl.): 177–179
8. Wakita K, Imahori Y, Ido T, et al (2000) Simplification for measuring the input function for ^{18}FDG-PET. Investigation of one-point blood sampling method. J Nucl Med 41:1484–1490
9. Mineura K, Sasajima T, Kowada M, et al (1997) Indications for differential diagnosis of non-tumor CNS diseases from tumors. A PET study. J Neuroimag 7:8–15

The Biology of Glioma—A Discussion from the Standpoint of Photodynamic Diagnosis and Photodynamic Therapy

Toshihiko Kuroiwa, Yoshinaga Kajimoto, Shin-ichi Miyatake, and Minoru Miyashita

Summary. Because it is difficult to prolong the survival of patients with malignant glioma, minimally invasive treatment is desirable when dealing with patients with this type of malignancy. This paper discusses the recently introduced technique of photodynamic diagnosis (PDD) and photodynamic therapy (PDT) using 5-aminolevulinic acid (5-ALA) for these patients. Oral administration with 5-ALA prior to surgery and application of 405 nm light to the tumor during surgery resulted in tumor-specific emission of red fluorescence (peak wavelength: 635 nm) reflecting protoporphyrin IX (a metabolite of 5-ALA). This technique of PDD was found to be very useful in achieving maximal tumor resection without hazardous sequel. PDT combined with prior PDD is thus promising as a means of treating malignant glioma.

Key words. biology, glioma, photodynamic diagnosis, photodynamic therapy, surgery

1 Introduction

Various treatment modalities for malignant glioma have not markedly prolonged the survival of patients. However, maximal surgical resection of the tumor has been shown to be an effective means of dealing with this malignancy. Surgery is therefore an important first step of treatment which determines the prognosis of patients with malignant glioma. Various methods have been developed for preoperative and intraoperative evaluation of the function of surrounding areas of the brain and intraoperative identification of the tumor. Fluorescent dyes are sometimes used for intraoperative identification of tumors which are depicted as contrast-enhanced lesions by computed tomography (CT) or magnetic resonance images (MRI). Methods using fluorescent dyes for intraoperative tumor identification include: (1) observation of dyes (e.g. fluorescein sodium) which have passed through the damaged blood brain

Department of Neurosurgery, Osaka Medical College, 2-7 Daigakumachi, Takatsuki, Osaka 569-8686, Japan

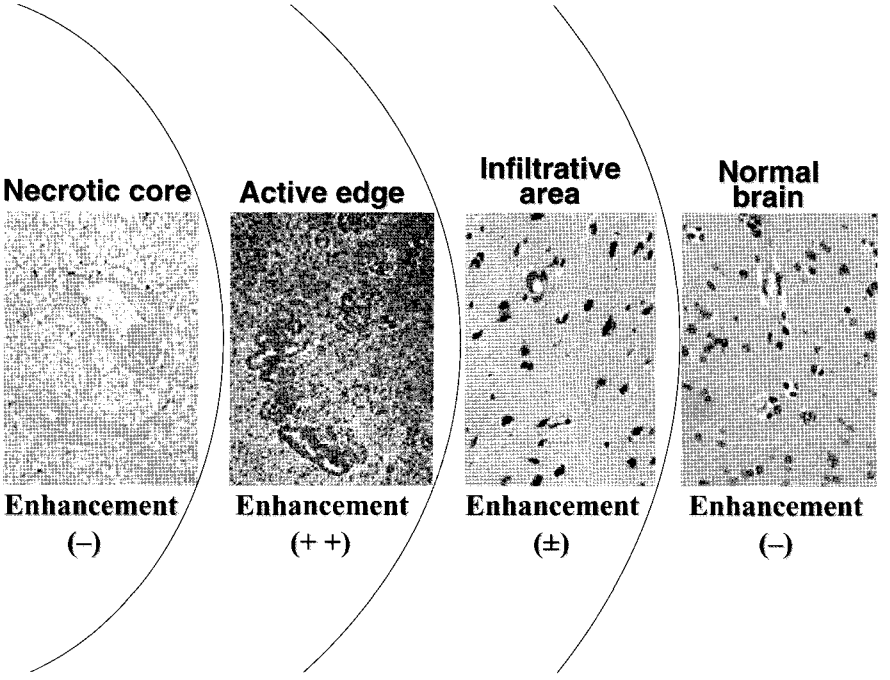


FIG. 1. Schematic diagram of the histology of glioblastoma multiforme

barrier (BBB) [1], and (2) observation of porphyrin derivatives (e.g. porfimer sodium) incorporated into tumor cells. For example, in cases of glioblastoma multiforme, both dyes emit fluorescence in the so-called "active edge" region (Fig. 1), and if surgical resection is confined to this region and to the necrotic area, the patient is unlikely to show postoperative deterioration of neurological symptoms. Thus, fluorescence-guided surgery is very useful in surgical treatment of malignant glioma. Recently, new photosensitizers such as 5-aminolevulinic acid (5-ALA) [2–4], 5-aminofluorescein-albumin [5] and mono-L-aspartyl chlorine [6] have been developed. This paper will focus on 5-ALA which has been increasingly used clinically.

2 Photodynamic Diagnosis (PDD) and Photodynamic Therapy (PDT)

The PDT technique has been recently used in some other specialties to provide minimally invasive therapy, and involves the excitation of porphyrin derivatives (specifically accumulated in tumor tissue) by light to allow selective destruction of tumor cells by free radicals (singlet oxygen, etc.) formed as a result of excitation. Porphyrin forms the basic framework of hemoglobin and plays an important physiological role. It has been reported that PDT destroys cells by means of apoptosis induced by the release of cytochrome C [6]. It has also been found that porphyrin accumulates in

tumor vessels. The anti-tumor effect of PDT therefore seems to involve injury and resultant obstruction of vessels which nourish the tumor. Studies of PDT for brain tumors began in the 1960s [7]. Reports on the clinical application of PDT to cases of glioma began to be published around 1980 [8]. In those days, porfimer sodium was primarily used in combination with 630 nm laser (excimer dye laser or YAG-OPO laser).

5-ALA has attracted interest recently. 5-ALA was first used clinically for PDT in the 1990s. In early clinical cases, 5-ALA was primarily administered topically for the diagnosis and treatment of tumors. Attempts to treat lung cancer by inhalation of 5-ALA, skin cancer by topical application of 5-ALA, and bladder cancer by intravesical infusion of 5-ALA have been reported, primarily from Europe. To date, few reports have been published concerning the clinical use of PDT with 5-ALA for the treatment of brain tumors, and more studies are needed to establish this therapy. However, intraoperative PDD using 5-ALA has been increasingly applied clinically [2–4]. 5-ALA is a heme precursor which is normally present in the human body. Two molecules of 5-ALA follow several steps of metabolism within the mitochondria to yield protoporphyrin IX (PpIX) (Fig. 2). PpIX then assumes the heme form in the presence of ferrochelatase and iron. If this process is disturbed, accumulation of PpIX occurs. In response to excitation (peak wavelength: 405 nm), PpIX emits fluorescence (peak wavelength: 635 nm). Therefore, if a filter allowing the passage of light at this excitation wavelength is used or if a laser is applied to the tumor, PpIX within the tumor is visible as red light (Fig. 3). The exact mechanism for specific accumulation of 5-ALA by tumor cells remains unknown, although several hypotheses have been proposed. One hypothesis is that 5-ALA is also taken up by normal cells (e.g. astrocyte), but it can be metabolize easily in these normal cells. At present, 5-ALA is available only as a reagent for research. However, since 5-ALA is normally present in the human body and because it can be administered orally, it can be used with relative safely. It has been reported that 5-ALA is likely to be degraded in the presence of alkalis. It is therefore advisable to avoid the use of antacids when 5-ALA is administered orally. Following an oral dose, the level of 5-ALA in tumor tissue reaches a peak at 2–6 h and decreases to zero in 12 h [9]. The molecular weight of 5-ALA is 167.6, slightly smaller than that of fluorescein sodium. 5-ALA can easily pass through the damaged BBB to reach a brain tumor. It is advisable to avoid preoperative use of steroids because steroids can disturb the transfer of 5-ALA to tumor tissue. Like other porphyrin derivatives, 5-ALA is contraindicated in cases of porphyria (a hereditary disease). 5-ALA is less likely to induce skin photosensitivity than the other porphyrin derivatives.

5-ALA is theoretically a very attractive substance because it is selectively accumulate by tumor cells. However, there are several problems associated with the use of 5-ALA. It usually cannot pass through the BBB (although some investigators have reported the passage of 5-ALA through an intact BBB [10]), and so it can only reach tumors when the BBB has been damaged. This means that 5-ALA is unlikely to reach tumor areas which are not depicted as contrast-enhanced areas by CT or MRI. Uptake of 5-ALA by brain tumor cells occurs only after successful passage of 5-ALA through the damaged BBB. In our experience, the intensity of fluorescence emitted from PpIX is not uniform even within the same tumor tissue, and in some cases of malignant brain tumors such as glioblastoma multiforme and metastatic brain tumor, no fluorescence is emitted. To overcome this phenomenon and to achieve reliable uptake of

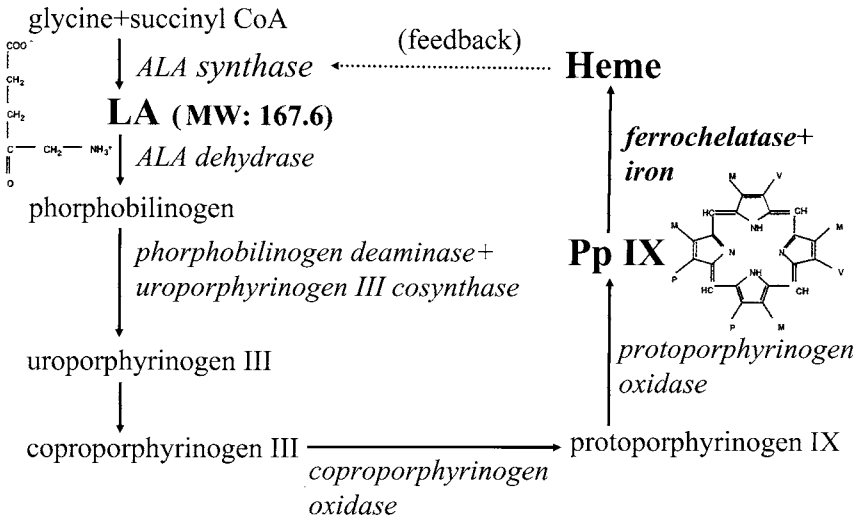


FIG. 2. A simplified systemic pathway from 5-aminolevulinic acid to protoporphyrin IX

FIG. 3. Photograph during surgery of glioblastoma multiforme. Left; normal image. Right; fluorescent image

5-ALA by tumor cells, it is important to clarify the mechanism for tumor uptake of 5-ALA. The sensitivity of 5-ALA in cases of malignant glioma is reported to be 60–85% [2,9], but the specificity of 5-ALA for tumor tissue is reported to be very high. However, we have found that fluorescence was also emitted by edematous or inflamed areas of the brain. The condition of the BBB seems to be a key factor determining the fate of 5-ALA in the brain.

3 Conclusion

PDD and PDT are promising techniques from the standpoint of minimally invasive neurosurgery. It is desirable to develop new photosensitizer which can easily pass through the BBB, are incorporated more selectively by tumor cells than existing pho-

tosensitizer, and can be excited by long wavelength light which is better transmitted by tissues.

References

1. Kuroiwa T, Kajimoto Y, Ohta T (1998) Development of a fluorescein operative microscope for use during malignant glioma surgery. A technical note and preliminary report. Surg Neurol 50:41–49
2. Stummer W, Novotny A, Stepp H, et al (2000) Fluorescence-guided resection of glioblastoma multiforme by using 5-aminolevulinic acid-induced porphyrins: A prospective study in 52 consecutive patients. J Neurosurg 93:1003–1013
3. Stummer W, Stepp H, Moller G, et al (1998) Technical principles for protoporphyrin-IX-fluorescence guided microsurgical resection of malignant glioma tissue. Acta Neurochir (Wien) 140:995–1000
4. Stummer W, Stocker S, Wagner S, et al (1998) Intraoperative detection of malignant gliomas by 5-aminolevulinic acid-induced porphyrin fluorescence. Neurosurgery 42:518–525
5. Kremer P, Wunder A, Sinn H, et al (2000) Laser-induced fluorescence detection of malignant gliomas using fluorescein-labeled serum albumin:Experimental and preliminary clinical results. Neurol Res 22:481–489
6. Argarwal ML, Caly ME, Harvey EJ, et al (1991) Photodynamic therapy induces rapid cell death by apoptosis in L5178Y mouse lymphoma cells. Cancer Res 51:5993–5996
7. Ransomoff HL, Carroll F (1966) Reaction of neoplasm and brain to laser. Arch Neurol 14:143–148
8. Peria C, Capuzzo T, Caggunaro G, et al (1980) First attempt at the photodynamic treatment of human gliomas. J Neurosurg Sci 24:119–129
9. Kaneko S (2001) Intraoperative photodynamic diagnosis of human glioma using ALA induced protoporphyrin. No Shinkei Geka 29:1019–1031
10. Olivo M, Wilson BC (2004) Mapping ALA-induced PP fluorescence in normal brain and brain tumour using confocal fluorescence microscopy. Int J Oncol 25:37–45

MCA Embolism Local Fibrinolytic Intervention Trial (MELT) Japan

Masayuki Ezura[1], Akira Takahashi[1], Yasushi Matsumoto[2], and Akira Ogawa[3]

Summary. MCA Embolism Local fibrinolytic intervention Trial (MELT) Japan started from January 2002. This study is a randomized controlled open trial for acute MCA embolism. Neurological criteria are NIHSS of 5 to 22 with the age ranging from 20 to 75. Those patients in whom LIF would not be started, if allocated, within 6 h after onset are excluded. Those who show no responsible findings or slight early ischemic change alone on CT scan are included. Allocation, LIF group or control group, is done via internet without time lag. LIF should be done using urokinase with a maximum dosage of 600,000 units in the LIF group. LIF should be finished within 1 h regardless the recanalization rate. Study size is 100 cases each and the primary endpoint is 0 to 2 in mRS at 3 month. Tentative analysis was done in those who completed 3 month follow-up, which was 45 cases in each group at March 2005. Primary endpoint of mRS 0 to 2 was 21/45 in control group while 18/45 in LIF group. Because of small number, it is not statistically significant, but they both are within estimated range. Further registration is strongly required.

Key words. cerebral embolism, fibrinolysis, MCA, MELT Japan, urokinase

Cerebral embolism is most difficult disease to treat among several types of stroke, because of sudden onset of disease and poor collateral flow with high mortality and morbidity rate. Although the National Institute of Neurological Disorders and Stroke rt-PA Stroke study [1] showed that iv-tPA within 3 h is better than conservative treatment, the efficacy and/or risk of local intraarterial fibrinolysis (LIF) is still unclear. To compare LIF to conservative treatment in the patient with middle cerebral artery (MCA) embolism, MCA embolism local fibrinolytic intervention trial (MELT) Japan has been conducted.

[1] Department of Neuroendovascular Therapy, Tohoku University, 2-1, Seiryo-cho, Aoba-ku, Sendai 980-8575, [2] Kohnan Hospital, Sendai, Japan and [3] Department of Neurosurgery, Iwate Medical University, Morioka, Japan

1 Materials and Methods

MELT Japan is a Japanese multi-center randomized controlled trial for MCA embolism, with a study size of 100 cases each in a control group and a LIF group [2,3]. The primary end point is modified Rankin scale 0 to 2 at 3 month after the onset. If the percentage of the patients fulfilling the primary end point is 20% better or more in the LIF group comparing to the control group, LIF is judged to be beneficial.

Inclusion criteria for this study are as follows: The patient should have MCA embolism including artery to artery embolism. Neurological state should be in between 5 and 22 of NIH stroke scale (NIHSS), and the age is in between 20 and 75 years. The diagnostic tool for ischemia is CT scan. MRI is prohibited. No or minimal early ischemic change, which is only in lenticular nucleus and/or Sylvian fissure, is acceptable. Those in whom LIF could be started within 6 h after onset and 2 h after CT scan are candidate for enrolling. The final decision should be made by cerebral angiography. If the angiography shows MCA embolic occlusion, allocation is done though the internet website, which is available for 24 h a day. Registry began in January 2002.

If the patient was allocated to the LIF group, LIF must follow diagnostic angiography. 6F introducing catheter is advanced to ipsi-lateral ICA under systemic heparinization. A microcatheter is introduced into or beyond the emboli though the introducing catheter using a micro guide wire. Urokinase is injected through the micocatether using infusion machine with a velocity of 120,000 IU/5 min. Every 120,000 IU, angiography should be done to confirm the degree of recanalization. Mechanical disruption by a microcatheter and/or a micro guide wire is accepted. Those procedures are repeated up to 600,000 IU or one hour. LIF must be finished in the following situation: (1) complete recanalization is achieved, (2) 600,000 IU of urokinase is given, (3) LIF procedure takes one hour long and (4) patients neurological condition significantly improves (NIHSS reduces 4 ranks and becomes under 4: e.g. ○ NIHSS 10 → 3, × NIHSS 7 → 4, × NIHSS 18 → 10).

2 Midterm Results

As of early March in 2005, 97 cases were registered from 40 sites. At that time, 90 cases were finished 3M follow-up. Table 1 demonstrates radiological findings between the LIF group and the control group. There is no significant difference in both groups. Onset to admission is 64 min in average, onset to CT scan is 107 min, and onset to allocation is 197 min. Table 2 demonstrates additional date of the LIF group. Onset to urokinase administration is 227 min and procedure time is 54 min. Two-thirds of the patients were given full dosage of urokinase. About a half patient showed more than 50% recanalization. Results regarding safety are shown in Table 3. Mortality was 3 in the LIF group, and 2 in the control group. Intracerebral hemorrhage was 5 in the LIF group, and 1 in the control group, brain edema was 2 in the LIF group and 1 in the control group, though they are not statistically significant difference. Results regarding efficacy are shown in Table 4. Primary end point was achieved in 21 patients in the LIF group, and 18 in the control group, this is also not stastically significant difference. Noticing mRS 0 or 1, which is one of the secondary end point, 17 patients are

TABLE 1. Radiological findings of both groups

	LIF group	Control group	*P* value
Occlusion point			
M1 proximal	14	11	
M1 distal	19	21	
M2	12	13	n.s.
Collateral			
Poor	9	16	
Moderate	24	18	
Rich	12	9	n.s.
Early ischemic sign in CT scan	18	21	n.s.

TABLE 2. Results of LIF procedure

Onset to UK	227 ± 61 min	
Procedure time	54 ± 21 min	
UK administered	0 IU	1
	<600,000 IU	14
	600,000 IU	30
Mechanical disruption	30 (67%)	
Recanalization	None	12
	<50%	10
	<100%	21
	100%	2

UK, urokinase.

TABLE 3. Safety of the study

	LIF group	Control group
Mortality	3	2
Intracerebral hemorrhage	5	1
Brain edema	2	1
Re-attack	4	0

TABLE 4. Efficacy of the study

Primary end point (mRS ≤ 2)		
LIF group	21/45 (46.7%)	
Control group	18/45 (40.0%)	n.s.
Secondary end point (mRS = 0,1)		
LIF group	17/45 (37.8%)	
Control group	9/45 (20.0%)	n.s.

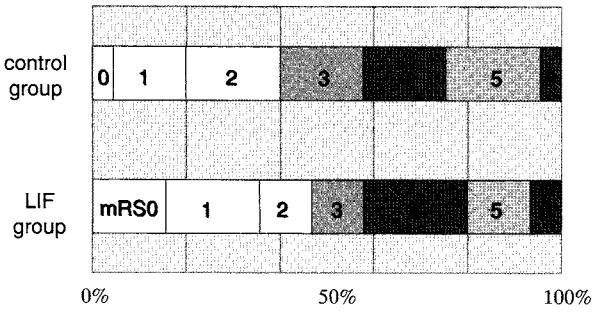


FIG.1. modified Rankin Scale at 3 months. Numbers 0 to 6 correspond to modified Rankin scales 0 to 6, respectively

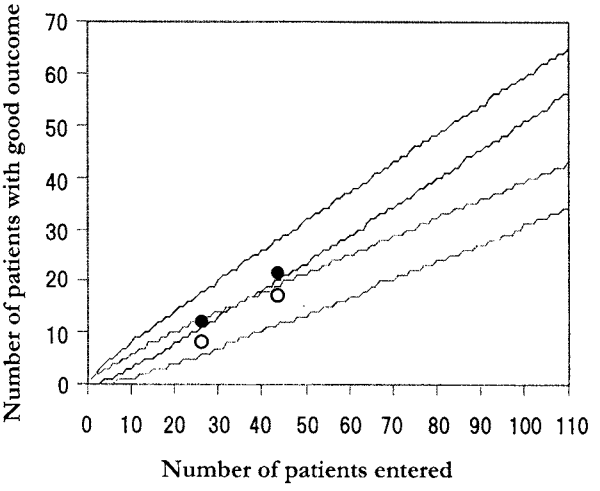


FIG.2. Estimated line and mid-term results. *Black lines* indicate estimated zone in the LIF group, and *gray lines* indicate in the control group. *Solid circles* indicate the results of the LIF group, and *open circles* indicate those of the control group

in the LIF group and 9 in the control group which is almost statistically significant. Modified Rankin scale at 3 months seems slightly better in the LIF group (Fig. 1). Figure 2 shows estimated line and the state at last year and present point. Both groups are within the estimated zone, though the difference is not so great.

3 Discussion

Comparing with Prolyse in Acute Cerebral Thromboembolism (PROACT) II [4], there are several differences (Table 5). PROACT II used Prourokinase and MELT Japan uses urokinase. MELT Japan was initially planned to use tPA, but Japanese Welfare Ministry did not permit to use tPA, because tPA was not approved to use cerebrovascular disease even now. Urokinase is approved only for intravenous 60,000 units a day. Indeed, 60,000 units a day is equal to nothing, but based on this fact, Japanese Welfare Ministry permit urokinase but tPA. Another difference is that mechanical disruption is accepted in MELT Japan, because there is no sponsorship from any drug companies.

TABLE 5. Comparison with PROACT II

	n	End point	Blinded follow-up	Baseline image	Drug	Mechanical disruption
PROACT II	180	mRS ≤2	Yes	CT	pro UK	Prohibitted
MELT Japan	200	mRS ≤2	Yes	CT	UK (≤600,000 IU)	Acceptable

mRS, modified Rankinscale; pro UK, prourokinase.

MELT Japan is still on-going study, so we cannot say anything from the mid-term result. However, if the registration cases increase in the similar manner, positive results will follow.

References

1. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group (1995) Tissue plasminogen activator for acute ischemic stroke. N Engl J Med 333:1581–1587
2. Ezura M, Matsumoto Y, Takahashi A (2004) Basics and standard of acute local intra-arterial fibrinolysis. Jpn J Neurosurg 13:111–115
3. Ezura M, Matsumoto Y, Takahashi A (2004) Acute local intraarterial fibrinolysis. Jpn J Stroke 26:599–602
4. Furlan A, Higashida R, Wechsler L, et al (1999) Intra-arterial prourokinase for acute ischemic stroke. The PROACT II studey: A randomized controlled trial. Prolyse in Acute Cerebral Thromboembolism. JAMA 21:2003–2011

Direct Cerebral Bypass Supplements Indirect Bypass Procedures in Moyamoya Disease

Yoshio Suzuki, Norikazu Hatano, Syuntaro Takasu, Noriaki Matsubara, Yugo Kishida, and Nobuhiko Mizutani

Summary. Moyamoya disease is a cerebrovascular disease characterized by cerebral hypoperfusion due to gradual stenosis/occlusion of major cerebral arteries at the base of brain with development of abnormal collateral circulation. The surgical treatment include direct and indirect bypass surgeries that are generally effective in improving cerebral hemodynamics and ischemic symptoms related to the disease. However, spontaneous vascularization after indirect surgery like simple encephaloduro-arterio-synangiosis (EDAS) may not support cerebral circulation adequately and, ischemic symptoms may persist even after surgery. In this prospective study, in 12 patients with moyamoya disease, in whom a sole indirect revascularization procedure failed to provide symptomatic relief, we performed direct and indirect bypass surgery simultaneously to increase cerebral blood flow (CBF). The combination of surgery consisting of both direct and indirect procedures covered the ischemic zone widely and postoperatively, the patients showed significant improvement in their symptoms.

Key words. moyamoya disease, indirect bypass surgery, ischemia, additional surgery

1 Introduction

Moyamoya disease is a unique disease of unknown etiology characterized by progressive occlusion of the supraclinoid portion of bilateral internal carotid arteries (IC), and the proximal portions of anterior (ACA) and middle cerebral arteries (MCA). Occlusion of the posterior circulation is also involved in 30–40% of patients. In most of the recommended procedures till date, either direct and/or indirect bypass surgery has been advocated to improve cerebral perfusion. In the present study, we performed combined surgery that included both the direct bypass procedures as well

Department of Neurosurgery, Nagoya Daini Red Cross Hospital, 2-9 Myoken, Showa, Nagoya 466-8650, Japan

as the indirect ones [1,2]. The combination of procedures ensured perfusion of a wider ischemic zone and salvaging of the penumbric area. Indirect procedures like encephalo-duro-arterio-synangiosis (EDAS), encephalo-myo-synangiosis (EMS) or galeal flaps are safe and easy. Direct bypass surgery, however, is more reliable in providing adequate cerebral blood flow but is technically difficult as the recipient artery running on the cortical surface is usually fine and fragile in moyamoya disease.

In 12 cases of moyamoya disease, an additional surgery after an indirect bypass procedure on one or both sides was required as the ischemic symptoms did not disappear after solely the indirect bypass surgery.

2 Clinical Material and Methods

2.1 Patient Spectrum

Over the past 20 years, more than 200 patients with moyamoya disease have undergone surgical management at our centre. In patients older than 5 years, combined surgeries including direct bypass surgery of superficial temporal (STA)-middle cerebral (MCA) or/and STA—anterior cerebral artery (ACA) anastomosis as well as indirect bypass procedures including EMS and galeal flap are being performed. In children less that 5 years, indirect bypass surgeries including EDAS, EMS and galeal flap are being performed since a direct bypass surgery is not feasible due to the small caliber of the anastomosing vessels.

The 12 patients included in this study had been referred to our hospital after undergoing an indirect bypass surgery elsewhere. An EDAS procedure using the parietal branch of STA had been performed in these cases. However, spontaneous revascularization between the placed STA and the brain vessels did not develop well and the ischaemic symptoms persisted.

2.2 Investigations

The existing cerebral blood flow (CBF), the territories of the infarction and the salvageable penumbric zones and the effectiveness of the indirect bypass surgery were evaluated using digital subtraction angiography (DSA), single photon emission computed tomography (SPECT), magnetic resonance imaging (MRI) with magnetic resonance angiography (MRA). In all these patients, following the EDAS procedure, CBF was only preserved around the STA and other areas showed hypoperfusion. In addition to bilateral internal carotid arteries, the ACA as well as the posterior cerebral (PCA) arteries were often occluded. Thus, the frontal and occipital regions supplied by these vessels remained grossly deficient in CBF despite the indirect bypass procedure. The entire posterior circulation was also not adequately covered through collateral circulation in these patients.

2.3 Surgical Procedure

In eight of these patients, the CBF was supplemented by adding both a direct bypass procedure using the frontal branch of STA and an indirect one using EMS with the

ipsilateral temporalis muscle. An occipital artery (OA)—PCA anastomosis was also done in two adult cases. Frontal and occipital galeal flap were also added in two pediatric cases (Table 1).

2.4 Surgical Nuances

The three main arteries in the scalp, the frontal and parietal branches of STA and the OA are available as donor arteries for the direct bypass surgery. As the parietal branch of STA had often been used for EDAS in these cases, the frontal branch of STA had to be utilized as a donor artery. The temporalis muscle, galeal tissue and reversed dural tissue were used as indirect donor material. The surgical planning involved selection of the best combination of these direct and indirect bypass procedures to optimize the ischaemic zone coverage. For example, we performed a direct anastomosis using the frontal branch of STA with placement of temporal muscle as EMS in the frontal area, and also placed a wide galeal flap on the occipital cortex concurrently to patients who had previously only received EDAS using the parietal branch of STA.

3 Results

All the 12 patients showed gradual improvement in their ischemic symptoms like recurrent attacks of headache or transient ischemic attacks (TIA) after the additional direct and indirect bypass surgeries. Clinical signs such as intelligence, daily activity and personal character improved in most of the cases. Their preoperative aggressive and hyperactive behavior transformed into a placid one and their concentration significantly improved following adequate revascularization.

The direct bypass surgery using the frontal branch of STA was effective in increasing CBF in the frontal area. EMS using the temporalis muscle was also effective in establishing a spontaneous anastomosis with the cerebral vasculature. Bifrontal and occipital galeal flaps in pediatric patients and in adults aged 40 years or less were effective in covering the frontal and occipital areas. TIAs of the visual field and weakness of bilateral lower limbs gradually decreased and finally completely resolved. The improvement in clinical symptoms was much faster and sustained after the direct bypass surgery.

The two adult patients in whom bilateral OA-PCA anastomosis was performed showed a slight improvement in clinical symptoms. Their follow-up MRA demonstrated a good patency through the newly established bypass routes. However, following the OA-PCA bypass procedure in one patient, CBF in the ACA area through PCA did not increase significantly at a follow up of one year. Perhaps the luminal diameter of the recipient blood vessel and connection between PCA and ACA also played an important role in the establishment of CBF of the revascularized ischemic zones.

Long-term follow-up of patients with MRI, MRA and SPECT demonstrated a gradual improvement of cerebral circulation at the sites of revascularization with disappearance of moyamoya vessels. However the disease itself was slowly progressive. Disappearance of moyamoya vessels also reduced the possibility of future occurrence of subarachnoid and intracerebral haemorrahge. In the cases where direct bypass

TABLE 1. Characteristics of the patients

Patient	Age	Duration	Previous ope	Symptoms	Decrease of CBF	Added ope	GOS
1	27	22	Lt EDAS	Mental deterioration	Frontal	Rt STA-ACA, STA-MCA + EMS Lt STA-MCA + EMS	GR
2	13	10	Bil EDAS	TIA, headache	Frontal & occipital	Bil STA-MCA EMS + OG	GR
3	12	11	Lt EDAS	Mental deterioration	Frontal	Rt STA-ACA STA-MCA + EMS Lt STA-MCA EMS + OG	GR
4	39	6	Bil EDAS	TIA	Frontal & occipital	Bil STA-MCA EMS + OG	GR
5	19	8	Lt EDAS	TIA	Frontal	Rt STA-MCA × 2 + EMS Lt observation	GR
6	22	13	Bil EDAS	TIA, depression	Frontal	Bil STA-MCA + EMS	GR
7	57	6	Rt EDAS	TIA	Frontal	Rt observation Lt STA-MCA EMS + FG	GR
8	41	2	Rt EDAS	TIA	Frontal & occipital	Rt observation Lt STA-MCA + FG	GR
9	38	4	Bil EDAS	TIA	Frontal & occipital	Bil OA-PCA	MD
10	60	13	Bil EDAS	Infarct, TIA	Frontal & occipital	Bil OA-PCA	GR
11	3	1	Bil EDAS	Infarct, TIA	Frontal & occipital	Bil FG	GR
12	14	4	Bil EDAS	TIA	Frontal & occipital	Bil FG + OG	GR

Age; year, Duration; year after previous surgery, CBF; the ischemic area on SPECT, FG; frontal galeal flap, OG; occipital galeal flap.

surgery was done successfully, the caliber of STA gradually expanded and the branches of MCA started filling and became clearly visible on DSA and MRA. Cerebral blood flow measurements with SPECT usually normalized in those areas of the brain where established infarction had not occurred and reactivity to acetazolamide steadily improved.

4 Discussion

Indirect bypass surgery like EDAS, EMS, galeal flap, reversed position of dural artery and multiple burr holes are more commonly used for surgical treatment of moyamoya disease than the direct bypass surgery. The former procedures facilitate the gradual development of spontaneous vascularization to the brain with improvement of CBF. Indirect bypass surgery is easy and safe, but less reliable when compared to the direct bypass surgery.

It is generally accepted that patients with moyamoya disease aged 40 years or more show less improvement with the indirect bypass procedures. Their relatively atrophic brain seems to poorly respond to the indirect bypass. Indirect surgery, therefore, is usually applied to the pediatric and young adult patients.

The preoperative investigative procedures are, however, not reliable indicators in identifying the subset of young patients who may be less sensitive to the indirect bypass. It is also difficult to predict the amount of deficiency in the CBF in the ischemic areas that will compensate through the indirect bypass routes.

When an indirect bypass surgery like EDAS does not provide sufficient increase in CBF, it is a serious problem for the patients. As the disease itself is progressive, ischemic symptoms like TIA persist and newer areas of infarction develop so that patients progressively deteriorate. These poor outcome patients have often received the surgical option of EDAS using only the parietal branch of STA that has only succeeded in perfusing a small area of the brain. In this study, we found that supplementing the bypass routes by additional surgical procedures is a very effective measure in combating progressive ischemia in these patients. The supplementing of EDAS using the parietal branch of STA with additional procedures like the frontal branch of STA for direct anastomosis, the temporal muscle for EMS, and occipital galeal flap or OA-PCA to cover the occipital area resulted in a significant increase in CBF over a wide area of the brain.

5 Conclusion

Bypass surgery can improve the hemodynamics in moyamoya disease, although the disease itself is progressive. Direct bypass surgery is more reliable in increasing CBF than the indirect bypass surgery. Combined direct and indirect surgical procedures should be applied to provide a comprehensive coverage to the ischemic area in patients with moyamoya disease.

References

1. Suzuki Y, Negoro M, Shibuya M, et al (1997) Surgical treatment for pediatric moyamoya disease: use of th3 superior temporal artery for both areas supplied by the anterior and middle cerebral arteries. Neurosurgery 40:324–330
2. Suzuki Y, Fujita M, Mizutani N, et al (2000) Role of nitric oxide in the control of cerebral microcirculation under physiological and pathological condition. Clin Hemorheol Microcirc 23:307–312

Treatment of Cerebral Vasospasm Following Subarachnoid Hemorrhage

Tadayoshi Nakagomi, Teruyuki Ishii, Hiroshi Nagashima, Toshihiro Mochizuki, Masahumi Hirata, Makiko Shirouzu, and Aya Kobayashi

Summary. In this paper, we analyzed the effect of cisternal washing therapy using urokinase combined with head shaking, which we introduced in 1994 for the prevention of vasospasm in patients with subarachnoid hemorrhage (SAH). A total of 280 consecutive cases with Fisher group 3 SAH since 1988 were retrospectively analyzed. Of these patients, 105 cases (56 cases (group A) before 1994 and 50 cases after 1994 (group B)) had not cisternal washing therapy, 174 cases after 1994 (group C), however, had this therapy. All of these patients had clipping surgery within 3 days following SAH, and had postoperative management both with normovolemia and with normo to mild hypertension. In these three groups, the incidences of symptomatic vasospasm, cerebral infarction on CT, and mortality and morbidity (M&M) due to vasospasm were analyzed. In the group A, the incidences of symptomatic vasospasm, cerebral infarction on CT, and M&M due to vasospasm were 7.1%, 33.9%, and 25%, respectively. In the group B, they were 2%, 20%, and 12%, respectively. On the other hand, in the group C, they were 4.6%, 5.2%, and 2.3%, respectively. This study demonstrated that cisternal washing therapy was effective to prevent cerebral infarction on CT and reduced M&M due to vasospasm.

Key words. subarachnoid hemorrhage, cerebral vasospasm, cisternal washing therapy, urokinase, head shaking

1 Introduction

Cerebral vasospasm is still one of the major causes of mortality and morbidity in patients with subarachnoid hemorrhage (SAH) [1]. In spite of extensive investigation to delineate the pathogenesis of vasospasm, the optimal treatment for vasospasm has

Department of Neurosurgery, Teikyo University School of Medicine, 2-11-1 Kaga, Itabashi, Tokyo 173-8605, Japan

not yet been established. Clinical studies have demonstrated the relationship between the location and volume of the subarachnoid clots and the incidence, distribution, and the severity of vasospasm [2,3]. In 1994, we started cisternal washing therapy using urokinase, combined with head-shaking in order to prevent cerebral vasospasm in patients with SAH [4]. In this paper, we retrospectively analyzed the effect of this method in preventing vasospasm in Fisher group 3 patients with SAH.

2 Materials and Methods

A total of 280 consecutive cases in Fisher group 3 on the preoperative CT, who had been admitted to Teikyo University Hospital since January 1988 to September 2004 were retrospectively analyzed. The patients were divided into 3 groups. Patients in group A were treated before 1994. Group B patients were treated after 1994, but had not cisternal washing therapy due to medical or surgical complication, problem in placement of the catheter, obstruction of the catheter with subarachnoid clots, and so on. Group C patient had cisternal washing therapy after 1994. Group A consists of 56 cases and group B 50 cases. Group C, which had cisternal washing therapy, consists of 174 cases.

All patients underwent clipping surgery within 3 days from the onset of SAH, and had postoperative management with normo-volemia and normo to mild hypertension. Soon after the craniotomy, a ventricular catheter was placed in the lateral ventricle. A draining catheter was placed in the carotid cistern or in the chiasmatic cistern. After the patients returned to the recovery room, cisternal washing therapy began by irrigating the subarachnoid space through these two catheters. Lactated Ringer solution which contains urokinase (60,000 IU/500 ml), was infused from the ventricular catheter at a rate of 60–180 ml/h. The pressure for cisternal irrigation was not set over a height of 25 cm H2O from the external auditory meatus. The intracranial pressure control system was usually set at a height of 5–10 cm H2O. Then, the head of the patient was rested on the head-shaking device (head-shaker), and was shaken periodically at the rate of 1 to 1.5 c/s. Almost all patients could tolerate head shaking up to 48 h. Cisternal washing therapy was terminated when the total amounts of urokinase reached 420,000 IU, or the high-density area in the Sylvian fissure disappeared on the CT. In recent protocol, this procedure is completed within 2–3 days.

In these three groups, the incidence of symptomatic vasospasm (transiently symptomatic vasospasm without infarction), cerebral infarction on CT. The outcome of the patients at 6 months following SAH, were assessed according to the Glasgow Outcome Scale. Overall mortality & morbidity (M&M) (below moderately disabled) due to vasospasm at 6 months following SAH were analyzed. Statistical analysis was done using Student's t-test or Chi-square test. The value were considered to be significant when $P < 0.05$.

3 Results

The age, gender distribution, preoperative WFNS grade, timing of surgery, and the site of aneurysm are shown in Table 1. The incidence of symptomatic vasospasm in groups A and B were 7.1 and 2.0%, respectively. In the patients who had not cisternal washing

TABLE 1. Summary of the cases

		Without CWT				With CWT	
		Group A		Group B		Group C	
Age							
	Range	35–69		16–87	Range	33–83	
	Mean	52.3		57.3	Mean	58.9	
Sex							
	M	21	37.5%	16	32%	M	67	38.5%
	F	35	62.5%	34	68%	F	107	61.5%
	Total	56		50		Total	174	
WFNS grade							
	I	27	37.5%	19	38%	I	62	35.6%
	II	20	35.7%	14	28%	II	51	29.3%
	III	7	12.5%	2	4%	III	11	6.3%
	IV	5	8.9%	7	14%	IV	31	17.8%
	V	3	5.3%	8	16%	V	19	10.9%
Timing of surgery							
	0	7	12.5%	18	36%	0	10	33.3%
	1	35	62.5%	20	40%	1	16	53.3%
	2	9	16.1%	7	14%	2	4	13.3%
	3	5	8.9%	5	10%	3	0	0.0%
Location							
	AC	31	55.3%	11	22%	AC	67	38.5%
	IC	13	23.2%	20	40%	IC	51	29.3%
	MC	12	21.4%	15	30%	MC	42	24.1%
	V-B	0	0.0%	4	8%	V-B	14	8.0%

CWT, cisternal washing therapy; AC, anterior cerebral artery; IC, internal cerebral artery; MC, middle cerebral artery; V-B, vertebrobasilar artery.

therapy, the incidence was 4.7% altogether (group A+B). In the group C, the incidence of symptomatic vasospasm was 4.6%. There was no significant difference in symptomatic vasospasm among the groups. Incidence of cerebral infarction on CT in groups A and group B were 33.9 and 28.0%, respectively. There was no significant difference in the incidence of cerebral infarction on CT between group A and B. In the patients who had not cisternal washing therapy, the incidence was 31.1% altogether (group A+B). On the other hand, in the group C, incidence of cerebral infarction on CT was 5.2%, which was significantly ($P < 0.05$) decreased.

Glasgow Outcome Scale at 6 months following SAH was shown in Table 2. Improvement in outcome in the group C is clearly noted.

In group A and B, incidence of M&M due to vasospasm were 25 and 12% respectively. It was 18.9% in the group without cisternal washing therapy (group A+B). On the other hand, in the group C, incidence of M&M due to vasospasm was 2.3%, which was significantly ($P < 0.05$) decreased.

4 Discussion

This study showed that after induction of cisternal washing therapy, incidence of cerebral infarction on CT, and M&M due to vasospasm were significantly decreased in the patients with SAH. According to the literature of more than 30,000 cases reviewed by

TABLE 2. Incidence of symptomatic vasospasm and clinical outcome

		Without CWT				With CWT	
		Group A		Group B		Group C	
Case							
		56		50		174	
Vasospasm							
	Symp only	4	7.1%	1	2%	Symp only	8	4.6%
	Infarction	19	33.9%	14	28%	Infarction	9	5.2%
	Total	23	41.0%	15	30%	Total	17	9.8%
GOS							
	GR	30	53.6%	25	50%	GR	132	75.9%
	MD	10	17.8%	9	18%	MD	15	8.6%
	SD	4	7.1%	4	8%	SD	9	5.2%
	V	4	7.1%	4	8%	V	8	4.6%
	D	8	14.3%	9	18%	D	10	5.7%
M&M							
	PBS	6	10.7%	11	22%	PBS	13	7.5%
	Med C	2	3.6%	3	6%	Med C	18	10.3%
	Surg C	4	7.1%	6	12%	Surg C	7	4.0%
	Vasospasm	14	25.0%	6	12%	Vasospasm	4	2.3%
	Total	26	46.4%	26	52%	Total	42	24.1%

CWT, cisternal washing therapy; GOS, Glasgow outcome scale; M&M, mortality and morbidity; GR, good recovery; MD, moderately disabled; SD, severely disabled; V, vegetative; D, death; PBD, primary brain damage; Med C, medical complication; Surg C, surgical complication.

Dolsch and King [1], symptomatic vasospasm or delayed ischemic neurological deficits (DINDs) occurred in 32.5% of the cases. Thirty percent of the patients with DIND died, and permanent neurological deficits occurred in 34% of the patients. In the present study, the incidence of symptomatic vasospasm and cerebral infarction on CT due to vasospasm in the group without cisternal washing therapy (group A+B) was 4.7% and 31.1%, respectively. The incidence of total symptomatic vasospasm (transiently symptomatic vasospasm without infarction and cerebral infarction) in the patients without cisternal washing therapy was almost the same as the incidence of symptomatic vasospasm reported by Dorsch and King. On the other hand, in the group with cisternal washing therapy, the incidence of symptomatic vasospasm and cerebral infarction on CT due to vasospasm was 4.6% and 5.2%, respectively. Although there was no significant difference in symptomatic vasospasm between the group without cisternal washing therapy (group A+B) and the group with cisternal washing therapy (group C), the incidence of cerebral infarction on CT due to vasospasm in group C decreased significantly ($P < 0.05$). There was no significant difference in the incidence of cerebral infarction on CT between group A and B. Decrease in cerebral infarction on CT, therefore, should be attributed to the cisternal washing therapy, not to the year when the patient has a treatment against cerebral vasospasm.

The present study also demonstrated that M&M due to vasospasm at 6 months following SAH, was 18.9% in the group without cisternal washing therapy (group A+B) and 2.3% in the group with cisternal washing therapy. Mortality and morbidity due to vasospasm decreased significantly ($P < 0.05$) in the group with cisternal washing therapy.

In conclusion, since the introduction of cisternal washing therapy, the incidence of cerebral infarction on CT, and M&M due to vasospasm was significantly ($P < 0.05$) decreased in Fisher group 3 patients with SAH. This method was effective to prevent cerebral infarction due to vasospasm. Therefore, cisternal washing therapy is recommended as a potent fibrinolytic therapy for the prevention of symptomatic vasospasm in thick SAH patients.

References

1. Dorsch NWC, King MT (1994) A review of cerebral vasospasm in aneurismal subarachnoid hemorrhage. J Clin Neurosci 1:19–26
2. Fisher CM, Kistler JP, Davis JM (1980) Relation of cerebral vasospasm to subarachnoid hemorrhage visualized by computerized tomographic scanning. Neurosurgery 6:1–9
3. Suzuki J, Komatsu T, Sato T, et al (1980) Correlation between CT findings and subsequent development of cerebral infarction due to vasospasm in subarachnoid hemorrhage. Acta Neurochir (Wien) 55:63–70
4. Nakagomi T, Takagi K, Narita H, et al (2001) Cisternala washing therapy for the prevention of cerebral vasospasm following aneurismal subarachnoid hemorrhage. Acta Neurochir 77:161–165

Retrocarotid Infracommunicating Approach for Parasellar and Interpedunclar Tumors

Hideyuki Ohnishi, Tatsuhiko Monobe, Yoshitaka Kamada, Naoto Adachi, Norimasa Kohaya, Kazuya Nakashima, Michio Nishikawa, and Katsushi Taomoto

Summary. We report a retrocaroted infracomminicating approach to parasellar and indepeduncular tumors. In a surgery for skull base legions, the most important points to prevent major complications are to preserve not only perforating arterial injuries but also venous injuries. In order to do the operation smoothly, the retrocarotid infracommunicating approach (tailored skull base approach) is quite useful.

Key words. retrocarotid infracommunicating space, parasellar tumors, surgical approach, microsurgery

1 Introduction

What is minimally invasive? There are many answers: for example less operation time, less blood loss, less damage to the brain, nerves and blood vessels and safety. I think the concept of minimally invasive neurosurgery is less complications and maximum efforts. Surgeons should evaluate the grade of complications preoperatively. High grade complications are death, consciousness disturbance, dementia, aphasia and hemiparesis. Medium grade complications are cranial nerve palsies. Low grade complications are cosmetic problems. In order to minimize major complications, we must avoid vascular injury first [1].

2 Operative Technique

The patient is placed supine on the operating table. The head is elevated about 15~20 degrees to horizontal plane. After a routine frontotemporal cranitomy is done, the orbitozygomatic osteotomy is followed. The medial sphenoid wing is removed

Hideyuki Ohnishi, Department of Neurosurgery, Ohnishi Neurological Center, Eigashima, Okubo-cho, Akashi, Hyogo, Japan

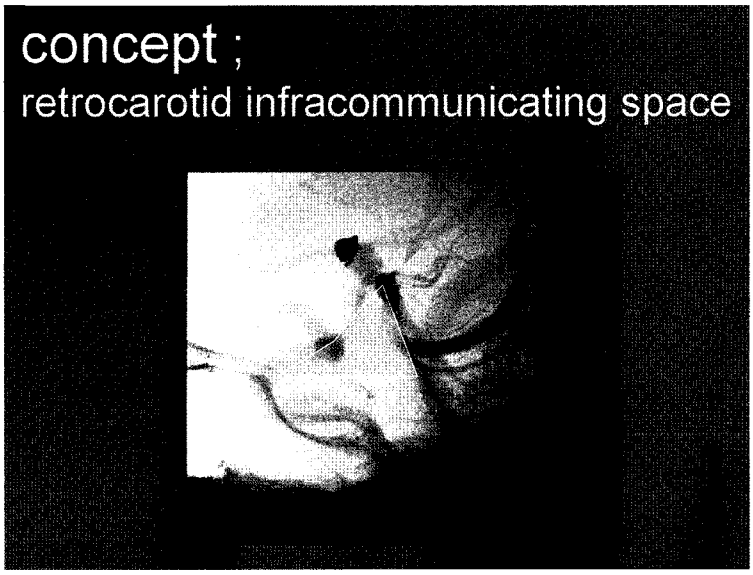


FIG. 1. The concept of retrocarotid infracommunicating space on carotid angiogram, lateral view

extradurally and superior orbital fissure is opened. The meningo-orbital band is cut and the temporal dura is peeled off from the inner cavernous membrane. The temporal lobe, the sylvian vein and the sphenoparietal sinus are mobilized together without disturbance of venous circulation. If the lesion is too large, optionally the anterior clinoid process is removed and the optic canal is unroofed. Sometimes the dural ring is opened in order to mobilize the internal carotid artery. When the lesion is extending down to the prepontine cistern, the anterior petroclinoidal fold is incised and separated from inner cavernous membrane. The third and fourth cranial nerves are mobilized.

There are many surgical approaches to the parasellar and interpeduncular lesions. Naming of these approaches is mainly based on the craniotomy. We emphasize the intracranial surgical corridor and how to develop the operative field. The concept of retocarotid infracommunicating approach is use the space which is consist of the internal carotid artery, the posterior communicating artery, the posterior cerebral artery and the anterior petroclinoidal fold (Figs 1 and 2). This space is widened by cutting the meningo-orbital band and peeling off the outer membrane of the cavernous sinus and mobilizing the temporal lobe and the internal carotid artery.

3 Representative Case

A 61 year-old male was admitted to our hospital complaining of headache and visual disturbances. A MRI showed the parasellar mass extending into the deep sylvian cistern, the interpedunclar cistern and the tentorial incisula regions (Fig. 3). The right

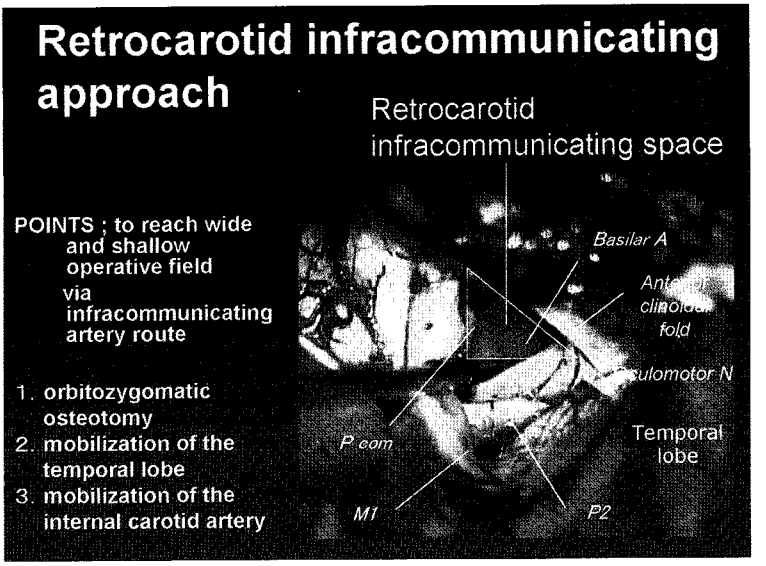


FIG. 2. A retrocarotid infracommunicating approach on operative view (Right pterional approach). This space consists of the internal carotid artery, the posterior communicating artery, the posterior cerebral artery and anterior petroclinoidal fold. This space is widened by cutting the meningo-orbital band and peeling off the outer membrane of the cavernous sinus, if necessary

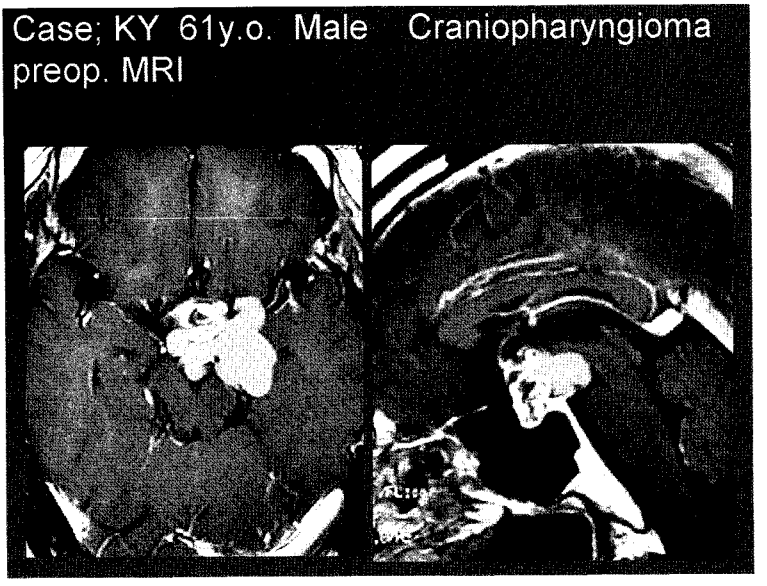
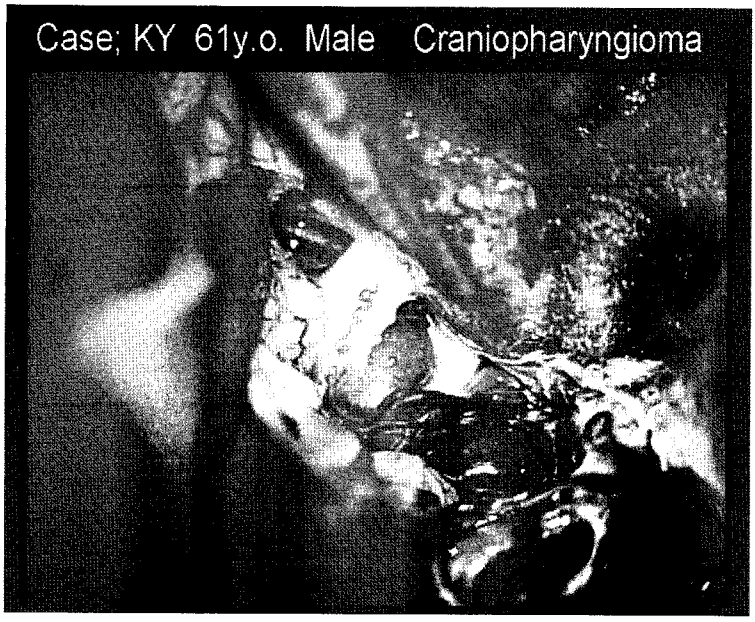
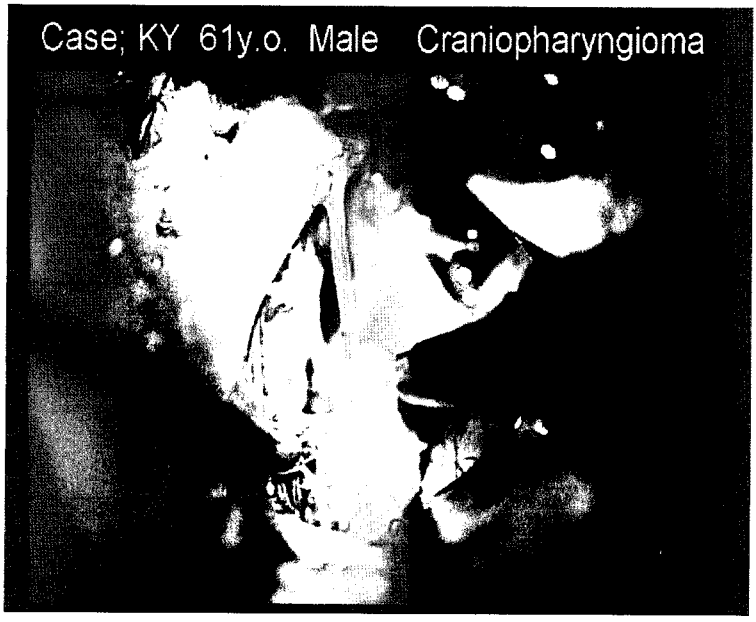


FIG. 3. Preoperative MRI of representative case

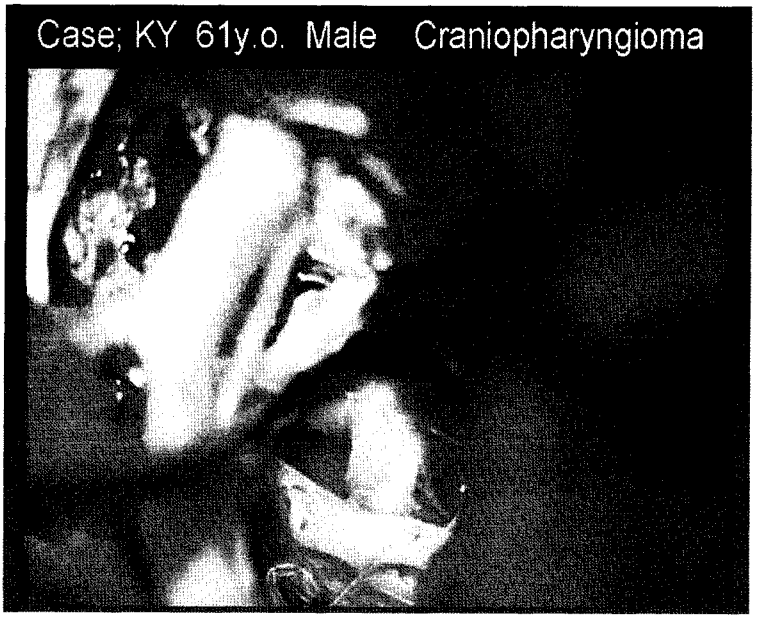


a

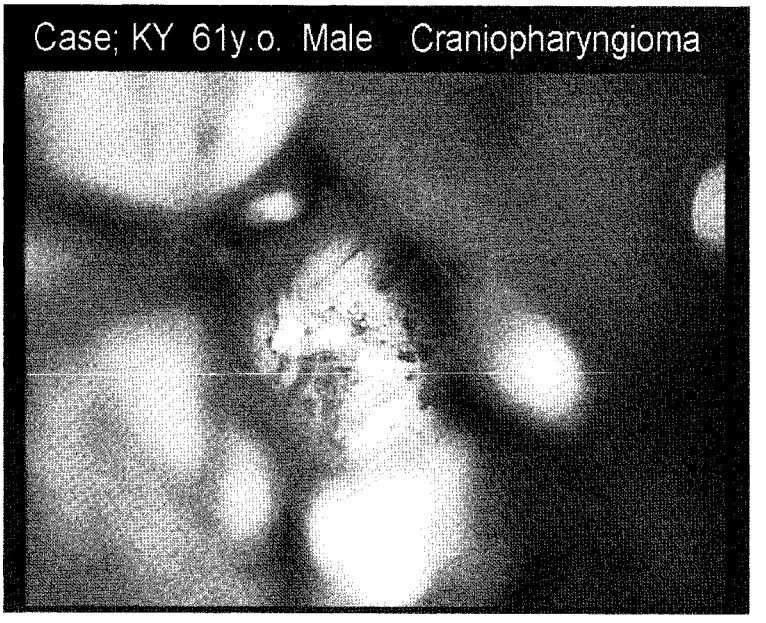


b

FIG. 4. Operative view. The right frontotemporal orbitozygomatic retrocarotid infracommunicating approach. The parasellar cisterns were filled with cystic part of the tumor (**a**). Perforating arteries were adhered to the tumor capsule (**b**). Arteries of the basal cisterns were dissected free. The solid part of the tumor was seen through the optico-carotid triangle (**c**). The tumor was totally removed. The ependyme of the third ventricle could be seen (**d**)



c



d

FIG. 4. *Continued*

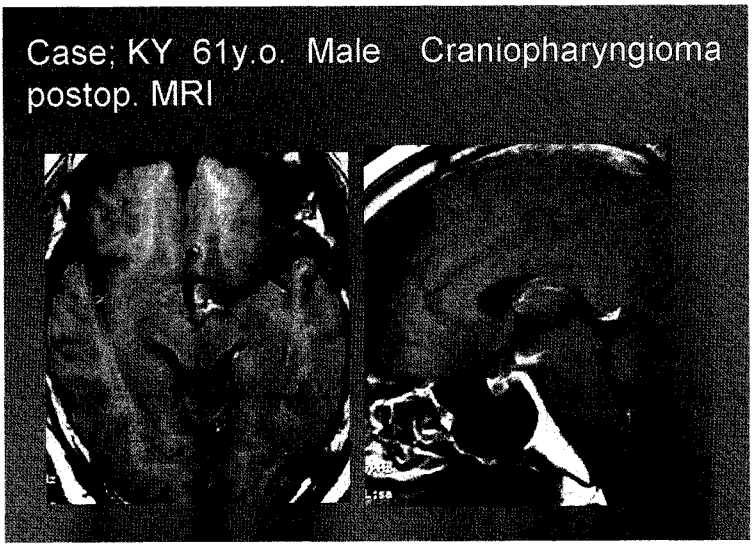


FIG. 5. Postoperative MRI showing no residual tumor

cerebral peduncle was compressed backward. The solid mass was extending into the sella turcica. The internal carotid artery, the posterior communicating artery, the anterior choroidal artery and perforating branches from these arteries were involved by the tumor.

Under the general anesthesia, the patient was placed supine and the head was rotated about 30 degrees and elevated about 20 degrees and extended to the axial plane become horizontal. The frontotemporal craniotomy and the orbitozygomatic osteotomy were done. The lateral surface of the cavernous sinus and the temporal lobe were mobilized posteriorlly together (Fig. 4**a**). The key point of this operation is to preserve all perforating arteries (Fig. 4**b**). These arteries dissected free and the tumor was totally removed (Fig. 4**c**,**d**). The patient discharged without complication except for diabetes insipidus which was controlled by intranasal desmopressin instillation. Postoperative MRI showed total removal of the tumor (Fig. 5).

4 Discussion

There are many surgical approaches to the parasellar and interpeduncular regions. When the lesion mainly located in midline structures, bifrontal basal interhemisphelic approach or interhemispheric approach may be selected. But in these approaches, lateral extending lesion could not be dissected and furthermore perforating arterial complication may easily be occurred. There are reports on the frontal pole veins injury in connecting with an anterior interhemispheric approach [2,3]. Tsutumi et al [2] reported that the venous infarction in the frontal lobe occurred in 11 (47.8%) of the 23 patients who underwent surgery in the acute stage of ruptured aneurysms.

Kageyama et al [4] used a pterional approach in 100 patients with aneurysm, and reported that postoperative cerebral injuries in the base of the frontal lobe were observed in 15% of the patients. They further reported that in many cases, such injuries to the brain occurred in patients in whom venous perfusion at the base of the frontal lobe flowed into the superficial sylvian vein, thus calling attention to the danger of venous perfusion trouble during the operation.

In the past, the superficial sylvian vein was usually cut in the approach for basilar artery aneurysms [5,6]. In this approach, however, we approached skull base lesions while preserving the superficial sylvian vein [1]. Day et al [7] reported on the extradural temporopolar approach for preservation of the temporal tip veins. Using their technique, preservation of the vein is possible but postoperative oculomotor and trochlear nerve palsies might easily occur. Since in our technique, these cranial nerves are not exposed, postoperative cranial nerve palsies did not occur. The lesions were sufficiently accessible without necessitating division of the SSV and temporal tip bridging veins, and we had no particular problems in using this technique.

References

1. Ohnishi H, Monobe T, Kamada Y, et al (1996) Preservation retrocarotid infracommunicating approach for parasellar and interpedunclar tumors. In: Hakuba A (ed) Surgery of the intracranial Venous System. Springer-Verlag, Tokyo, pp 380–385
2. Tsutumi K, Shiokawa Y, Sakai T, et al (1991) Venous infarction following the interhemispheric approach in patients with acute subarachnoid hemorrhage. J Neurosurg 74:715–719
3. Oka K, Hashiomoto T, Tomonaga M, et al (1991) A significance of the frontopolar vein for anterior interhemispheric approach. Surg Cereb Stroke 19:51–54
4. Kageyama Y, Fukuda K, Kobayashi S, et al (1992) Cerebral vein disorder and postoperative brain damage associated with the pterional approach in aneurysm surgery. Neurol Med Chir (Tokyo) 32:733–738
5. Heros RC, Lee SH (1993) The combined pterional/anterior temporal approach for aneurysms of the upper basilar complex: Technical report. Neurosurgery 33:244–251
6. Sano K (1980) Temporo-polar approach to aneurysms of the basilar artery at and around the distal bifurcation: Technical note. Neurol Res 2:361–367
7. Day JD, Giannotta SL, Fukushima T (1994) Extradural temporopolar approach to lesions of the upper basilar artery and infrachiasmatic region. J Neurosurg 81:230–235

Genetically Modified Cell Line Grafting for the Treatment of Parkinson's Disease

Isao Date, Tetsuro Shingo, and Takao Yasuhara

Summary. Neural transplantation is one of the newest therapeutic approaches for the treatment of Parkinson's disease. Many types of donor cells have been investigated in order to deliver neurotransmitter and neurotrophic factors into the brain. Merits of using cell line as donor cells are that they are unlimited theoretically and genetic manipulation is easy to be performed. When cell line is encapsulated into the hollow fiber consisted of semipermeable membrane, immunological rejection and tumor formation can be avoided. PC12 cells have been commonly used as dopamine secreting cell line and many types of neurotrophic factor secreting cell lines have been established using molecular biology techniques and grafting these cell lines demonstrated neuroprotective effect on host dopaminergic neurons. New approaches using cell line grafting are simultaneous delivery of dopamine and neurotrophic factor, usage of human-derived cell line for grafting and control of dopamine secreting after grafting into the brain. These new methods are important to consider future clinical application of cell line grafting for the treatment of Parkinson's disease.

Key words. Parkinson's disease, neural transplantation, cell line, neurotransmitter, neurotrophic factor

1 Introduction

Parkinson's disease is a neurological disorder characterized by chronic progressive degeneration of nigrostriatal dopaminergic system. Although stereotactic surgery such as deep brain stimulation has been performed as surgical therapy, intracerebral cell grafting attracts increasing attention as new surgical therapy. In this review, genetically modified cell line grafting for the treatment of Parkinson's disease will be summarized.

Department of Neurological Surgery, Okayama University, 2-5-1 Shikata-cho, Okayama 700-8558, Japan

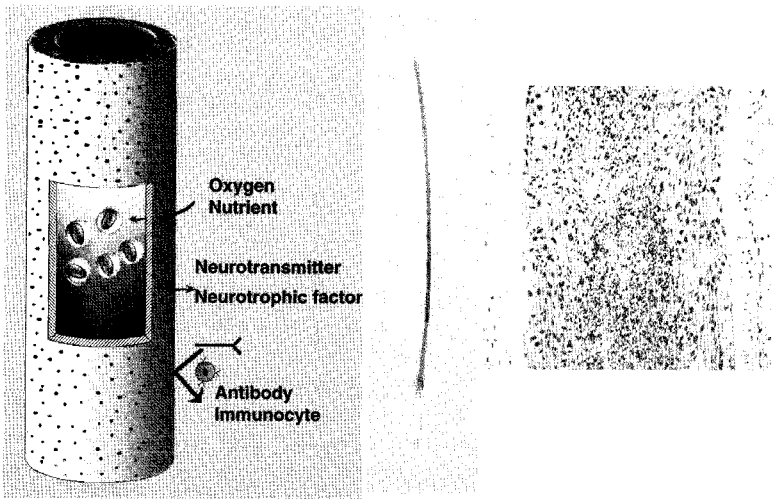


FIG. 1. Encapsulated cell line grafting. Cells are encapsulated into the hollow fiber consisted of semipermeable membrane. Oxygen and nutrients can enter the capsule and neurotransmitters and neurotrophic factors secreted from the cells can be delivered from the cells freely, but antibodies and immunocytes cannot enter the capsule, thus, the cells inside are immunologically isolated (left). By attaching silicone tether, these capsules can be retrieved at any time after grafting, showing the safety of this procedure (middle). Histology of the retrieved capsule 12 months after grafting shows very good survival of encapsulated cells (right)

2 Encapsulated Cell Line Grafting

The merits of using cell line as donor cells for intracerebral grafting are that they are unlimited theoretically and genetic manipulation is easy to be performed. At the present time, because most of the cell lines as stable source of neurotransmitters and neurotrophic factors are derived from species other than humans, immunological rejection and tumor formation are the main issues to be solved. In order to overcome these issues, cell lines have been encapsulated into the hollow fiber consisted with semipermeable polymer membrane and grafted into the host brain; basic studies as well as clinical application have been published [1,2]. Because the capsule is semipermeable, oxygen and nutrients can be provided into the capsule and neurotransmitters and neurotrophic factors can be secreted from the capsule, but antibodies or immunocytes cannot get into the capsule, thus, the inside of the capsule is immunologically isolated. In addition, rigid nature of the capsule can prevent tumor formation of the cells. By attaching silicone tether, the capsule can be retrieved from the brain whenever necessary showing the safety of this procedure (Fig. 1).

3 Neurotransmitter Secreting Cell Line Grafting

As dopamine secreting cell line, PC12 cells, which are derived from rat pheochromocytoma, have been most commonly used as donor cell line. It has been confirmed that

when PC12 cells are grafted into the striatum of parkinsonian model rats the host animals demonstrated histological, neurochemical and behavioral recovery. When PC12 cells were grafted into the xenogeneic monkey brain without encapsulation, these cells were completely rejected by 8 weeks after grafting which were confirmed by MRI and histological analysis [3]. We have performed long-term primate study using encapsulated PC12 cells for the treatment of Parkinson's disease [4]. Left intracarotid injection of MPTP, which is a neurotoxin for dopaminergic neurons, was performed to make hemiparkinsonian model monkey. Encapsulated PC12 cells were grafted into the left striatum. Neurochemical analysis revealed that dopamine secretion from the grafted capsules was maintained for 12 months and histological analysis demonstrated very good survival of grafted PC12 cells at 12 months after grafting. Although immunosuppressant was not administered, there were no signs of immunological rejection in the host brain and reactive gliosis surrounding the capsule was minimal. Hematological analysis did not show abnormality in the white blood cell count and CD4/CD8 value. The monkeys receiving encapsulated PC12 cells showed behavioral improvement for 12 months. Similar experiment was published from other laboratory and positron emission tomography (PET) showed dopamine secretion from the grafted PC12 capsule [5].

4 Neurotrophic Factor Secreting Cell Line Grafting

It has been reported that protection and repair of neurons can be expected by intracerebral administration of neurotrophic factors for various neurological disorders. Meanwhile, it is now possible to establish cell lines secreting various types of neurotrohpic factors due to the development of molecular biology techniques. When these cell lines are encapsulated and grafted into the brain, stable delivery of neurotrophic factors can be achieved.

Intracerebral grafting of cell lines secreting neurotrophic factors such as nerve growth factor (NGF), ciliary neurotrophic factor (CNTF), glial cell line-derived neurotrophic factor (GDNF), basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF) has been reported so far [1,6–9].

GDNF is a potent neurotrophic factor for dopaminergic neurons. We established a cell line secreting GDNF by using genetic manipulation, encapsulated this cell line and grafted in the right striatum of host rats. The host rats received 6-hydroxydopamine (6-OHDA), which is a neurotoxin for dopaminertic neurons, in the right striatum either before or after transplantation of GDNF secreting cell line and long-term evaluation was peformed. GDNF was secreted continuously from the grafted capsule for the period of 6 months and good survival of GDNF secreting cells has been obtained in the capsule. Good survival and regeneration of host dopaminergic fibers in the striatum and dopaminergic cell bodies in the substantia nigra were observed and host animals showed behavioral recovery [7,10].

5 Simultaneous Delivery of Neurotransmitter and Neurotrophic Factor by Cell Line Grafting

Regarding cell grafting for Parkinson's disease, activation of host intrinsic dopaminergic system by delivering neurotrophic factors from the grafted cells has been inves-

tigated in addition to dopamine replacement from the grafted cells. Although these approaches have been performed separately thus far, we are trying to deliver both dopamine and GDNF simultaneously by using encapsulated cell line grafting technique.

We have established a cell line named PC12-GDNF by inserting GDNF gene into the PC12 cells with cationic liposome method. Although conventional PC12 cells secrete dopamine in a stable fashion but do not secrete GDNF, newly established PC12-GDNF cell line secrete both dopamine and GDNF. When PC12-GDNF cell line was grafted into the parkinsonian model rats, the animals demonstrated histological, neurochemical and behavioral recovery.

As shown above, more effective therapy can be provided if simultaneous delivery of neurotransmitters and neurotrophic factors into the host brain is achieved.

6 Intracerebral Grafting of Human-derived Cell Line

When we consider clinical application of intracerebral grafting of cell lines secreting neurotransmitters and neurotrophic factors, it is essential to investigate using human-derived cell lines. Human amniotic epithelial cells are one group of cells which have been studied for the purpose of cell grafting and regenerative medicine [11]. These cells are known to secrete neurotrophic factors such as dopamine and acetylcholine and various types of neurotrophic factors.

The human amniotic epithelial cell line was immortalized, encapsulated and grafted into the striatum of unilateral parkinsonian model rats. Dopamine was continuously secreted from the grafted capsule and bFGF and transforming growth factor-beta (TGF-beta), which are neurotrophic factors for dopaminergic neurons, were also secreted from the capsule. The regenerative effect of the graft on the host dopaminergic system and functional recovery of the host were observed.

These studies demonstrate that human-derived cell line can be grafted into the brain by using encapsulation technique without immunological rejection and tumor formation.

7 Control of Neurotransmitter and Neurotrophic Factor Secretion after Grafting into the Brain

When we perform intracerebral grafting of cell lines, it would be ideal if the amount of neurotransmitters and neurotrophic factors can be controlled after grafting. The authors established a new cell line named PC12th Tet-Off cells; the amount of dopamine secreted from PC12th Tet-Off cells can be controlled by stimulation from outside. By inserting genes of tyrosine hydroxylase which is a limiting enzyme for dopamine production under Tet-Off regulatory system, the amount of dopamine production can be controlled when tetracycline or its analog doxycycline is added from outside. In vitro study showed that dopamine secretion from PC12th Tet-Off cells could be reduced by adding doxycycline into the culture media in a doze dependent fashion. Moreover, when encapsulated PC12th Tet-Off cells were grafted into the striatum of parkinsonian model rats, the apomorphine-induced rotational behavior could be controlled by administration of doxycycline to the hosts.

Because control of neurotransmitter and neurotrophic factor secretion from the cell line after grafting can be achieved, the issues related to the clinical application of cell line grafting have been gradually overcome.

8 Conclusion

The idea of using cell line as donors has been popular among researchers in the field of neural transplantation, but how to control immunological rejection and tumor formation has been important issue to be solved. Because encapsulated cell line grafting has been available and various types of cell lines secreting neurotransmitters and neurotrophic factors can be created using genetic manipulation, the research using this technique is expected to develop as one of the potential therapy for many neurological disorders including Parkinson's disease.

The encapsulated cell grafting technique has safety because the grafts can be retrieved very easily from the host brain after grafting when necessary. When clinical application of cell transplantation using embryonic stem (ES) cells or other types of stem cells will be performed, encapsulated cell grafting technique can be used as a first step in order to show the safety of using those cells for grafting purposes.

References

1. Aebischer P, Schluep M, Deglon N, et al (1996) Intrathecal delivery of CNTF using encapsulated genetically modified xenogeneic cells in amyotrophic lateral sclerosis patients. Nat Med 2:696–699
2. Emerich DF, Winn SR, Christenson L, et al (1992) A novel approach to neural transplantation in Parkinson's disease: Use of polymer-encapsulated cell therapy. Neurosci Biobehav Rev 16:437–447
3. Yoshida H, Date I, Shingo T, et al (2003) Stereotactic transplantation of a dopamine-producing capsule into the striatum for treatment of Parkinson disease: A preclinical primate study. J Neurosurg 98:874–881
4. Date I, Shingo T, Yoshida H, et al (2000) Grafting of encapsulated dopamine-secreting cells in Parkinson's disease: Long-term primate study. Cell Transplant 9:705–709
5. Subramanian T, Emerich DF, Bakay RA, et al (1997) Polymer-encapsulated PC-12 cells demonstrate high-affinity uptake of dopamine in vitro and 18F-Dopa uptake and metabolism after intracerebral implantation in nonhuman primates. Cell Transplant 6:469–477
6. Date I, Shingo T, Ohmoto T, et al (1997) Long-term enhanced chromaffin cell survival and behavioral recovery in hemiparkinsonian rats with co-grafted polymer-encapsulated human NGF-secreting cells. Exp Neurol 147:10–17
7. Date I, Shingo T, Yoshida H, et al (2001) Grafting of encapsulated genetically modified cells secreting GDNF into the striatum of parkinsonian model rats. Cell Transplant 10:397–401
8. Fujiwara K, Date I, Shingo T, et al (2003) Reduction of infarct volume and apoptosis by grafting of encapsulated basic fibroblast growth factor-secreting cells in a model of middle cerebral artery occlusion in rats. J Neurosurg 99:1053–1062
9. Yasuhara T, Shingo T, Kobayashi K, et al (2004) Neuroprotective effects of vascular endothelial growth factor (VEGF) upon dopaminergic neurons in a rat model of Parkinson's disease. Eur J Neurosci 19:1494–1504

10. Shingo T, Date I, Yoshida H, et al (2002) Neuroprotective and restorative effects of intrastriatal grafting of encapsulated GDNF-producing cells in a rat model of Parkinson's disease. J Neurosci Res 69:946–954
11. Uchida S, Suzuki Y, Araie M, et al (2003) Factors secreted by human amniotic epithelial cells promote the survival of rat retinal ganglion cells. Neurosci Lett 341: 1–4

Controlled Secretion of β-endorphin from Human Embryonic Kidney Cells Carrying a Tet-on-NL1-β-endorphin Fusion Gene: Gene Therapy of Pain

YOUICHI SAITOH[1], YUTAKA EGUCHI[2], TOSHIKI YOSHIMINE[1], and GUY BOILEAU[3]

Summary. Cell therapy with polymer capsules has been developed for CNS diseases, and has great potential advantages, including constant delivery of the products and avoidance of rejection by the host immune system. To control gene expression of transfected cells in the capsule exogenously, Tet-on system was applied. Under this system, addition of Dox to cells increases the expression of genes. And to obtain the cell line secreting human β-endorphin, we designed a new gene construction. We fused the sequences of human β-endorphin to the N-terminal 63 amino acid residues of NL1. NL1 is a type II membrane protein as a member of the neprilysin family. The stable transfectant (HEK[pTet-NL1-endo] cells) secreted appreciable amounts of β-endorphin. Since gene expression in the cells can be regulated by the Tet-on system, HEK[pTet-NL1-endo] cells (1.0×10^6 cells) which were seeded in 35-mm-diameter dishes, and treated for 24 h with Dox at concentrations of 1,000, 100, 50, 20, 10, 1.0 or 0 ng/ml. HEK[pTet-NL1-endo] secreted β-endorphin in a dose-dependent manner upon Dox addition. In our previous study, we showed a dose-dependent secretion of ACTH from encapsulated Neuro2A-POMC cells implanted in vivo in the CSF of rats, upon administration of Dox to host peritoneum space. Thus it can be envisaged that HEK[pTet-NL1-endo] cells, encapsulated and transplanted in the CSF of host animals, would secrete β-endorphin according to the various amounts of administered Dox.

Key words. tetracycline, Tet-on system, β-endorphin, pain, NL1

Cell therapy with polymer capsules has been developed for central nervous system diseases [1], such as Parkinson's disease [2], amyotrophic lateral sclerosis [3] and cancer pain [4,5]. The use of encapsulated cells has great potential advantages, including constant delivery of the products and avoidance of rejection by the host immune

Departments of [1]Neurosurgery and [2]Post-genomics & Diseases, Osaka University Medical School, 2-2 Yamadaoka, Suita, Osaka 565-0871, Japan; and [3]Department of Biochemistry, Faculty of Medicine, University of Montreal, Quebec, Canada

system. An ability to control the expression levels of products in cell transplantation therapy would provide further significant advantages. Ideally, transfected genes in the implanted grafts should be regulated intrinsically, leading to delivery of neuropeptides or transmitters on demand. A practical alternative might be to control gene expression of transfected cells exogenously. Several attempts to control gene expression in such cells have been reported, i.e., regulation by steroid hormones [6], isopropyl β-D-thiogalactoside [7], and heavy metals [8], but most of these substances may induce serious side effects *in vivo*.

More recently, a transcriptional trans-activator, rtTA, was developed by fusing the VP16 activation domain with a mutant tetracycline (Tet) repressor from *Escherichia coli* [9]. This trans-activator requires Tet derivatives such as doxycycline (Dox) to bind a specific target sequence, tet operator. Thus, addition of Dox to cells that constitutively synthesize rtTA was reported to increase the expression of genes under the control of rtTA by more than 1,000-fold. This system is called the "Tet-on system". A "Tet-off system" is also available, in which the addition of Dox decreases gene expression. The Tet-on system appears to be better suited for mammalian cells for regulated production of the interested peptides: (1) gene expression is easily regulated by administration of Dox, (2) Dox is minimally toxic and (3) Dox does not activate other cellular genes. Since pain treatment by cell transplantation, for example, would require appropriate control of opioid delivery, the Tet-on system is suitable.

Proopiomelanocortin (POMC) gene is the structural gene for β-endorphin, a potent endogenous opioid peptide. The POMC gene produces a precursor protein, POMC, that is processed by prohormone convertases located in the secretory pathway into several bioactive peptides including ACTH, β-lipotropin, α-MSH, and β-endorphin. The mouse neuroblastoma cell line (Neuro2A) possesses these converting enzymes, so that cells transfected with swine POMC cDNA secreted ACTH and β-endorphin [10]. When these transfected cells were encapsulated in polymer capsules and transplanted into rat CSF space, the animals demonstrated analgesia to the analgesimetric test [5]. However, it is important that regulated amounts of opioids are transfused into the CSF space.

In a previous study we showed that induced secretion of β-endorphin can be obtained upon administration of Dox when the POMC cDNA was expressed in Neuro2A cells under the regulation of Tet-on system [11,12]. Peptide secretion was quickly increased by Dox administration, and maximum amount of the secreted peptide was obtained after 36-h incubation. The continuous and intermittent administration of Dox was valid for a month, when encapsulated Neuro2A-POMC cells were used [11]. After withdrawal of Dox, 4 days were enough to return to the pre-treated level [12]. Thus, Tet-on system seems to be suitable to regulate the secretion of opioid peptide from cells. However, these Neuro2A-POMC cells secreted not only β-endorphin but also ACTH, and the amounts of secreted β-endorphin were relatively low because of unknown reasons. To overcome these problems, we designed a new gene that fulfilled the following criteria: (1) the fusion gene product should be targeted to the ER to enter the secretory pathway, (2) the fusion protein should be processed in most cells and (3) only β-endorphin should be secreted without any other peptides.

To achieve these goals, we constructed a new fusion gene system. Because β-endorphin itself has no signal sequence required for its secretion, we fused the

sequences of human β-endorphin to the N-terminal 63 amino acid residues of NL1. NL1 is a type II membrane protein cloned from mouse testis as a member of the neprilysin family of cell surface zinc metallopeptidases [13]. Although other family members are cell surface enzymes, NL1 has a putative convertase cleavage site in its ectodomain (Arg-Thr-Val-Val-Lys-Arg_{63}), and the protease domain downstream of the convertase cleavage site was secreted efficiently as a soluble enzyme in the culture medium when overexpressed in HEK293 cells [13]. Furin or other subtilisin-like convertases seem to be responsible for processing of NL1 in HEK293 cells [13]. Therefore, any peptide sequences that are joined to just downstream of the convertase cleavage site would be cut off and released in cells expressing the convertase. In addition, the NL1 N-terminal fragment also contains the short N-terminal cytoplasmic tail and the transmembrane anchor region that also acts as an ER targeting signal. This NL1 fragment would remain associated with the plasma membrane upon cleavage of the β-endorphin sequence, thus resulting in secretion of the opioid peptide only. The detailed gene constructions were already reported [14].

HEK293 cells were co-transfected with pTet-NL1-endo and Tet-on system. The obtained stable transfectant (HEK[pTet-NL1-endo] cells) secreted appreciable amounts of β-endorphin. Since gene expression in the cells can be regulated by the Tet-on system, we next examined the ability of Dox to induce β-endorphin expression in cultured HEK[pTet-NL1-endo] cells. HEK[pTet-NL1-endo] cells (1.0×10^6 cells) maintained in Dulbecco's modified eagle's medium containing 5% fetal bovine serum and geneticin (1.0 mg/ml; GIBCO-BRL, Grand Island, NY) were seeded in 35-mm-diameter dishes, and treated for 24 h with Dox at concentrations of 1,000, 100, 50, 20, 10, 1.0 or 0 ng/ml. The amounts of β-endorphin secreted in the medium were measured with a specific radioimmunoassay using an anti-β-endorphin immunoglobulin G originally raised in rabbits that received several subcutaneous injections of synthetic human β-endorphin [5,12]. β-endorphin was not detectable in medium after culture of HEK293 cells that were not transfected. Similar to results obtained previously with Neuro2A-POMC cells [12], HEK[pTet-NL1-endo] secreted β-endorphin in a dose-dependent manner upon Dox addition (Fig. 1). The variations due to linear contrast was significant ($P < 0.0001$) and positive linear trend of the concentration of β-endorphin with respect to Dox was suggested. The cells secreted only 53.8 pg of β-endorphin per milliliter without Dox treatment, but the amount of secreted β-endorphin reached 342.8 pg/ml in the presence of 1,000 ng/ml Dox and 303 pg/ml in the presence of 10,000 ng/ml. The plateau level of β-endorphin secretion was observed over 1,000 ng/ml Dox, which was almost same phenomenon as previous reports [12,15]. We observed a 5.8-fold induction over the range of Dox concentrations used. These results indicate that the level of β-endorphin secretion can be controlled by the administration of Dox at various concentrations.

In the present study, we have shown that β-endorphin can be secreted from cells transfected with the fusion gene containing β-endorphin coding sequence joined to just downstream of the convertase cleavage site of N-terminal portion of NL1 gene. This system should be great help to construct cells that secrete the peptide of interest. We also have shown that the concentration of secreted β-endorphin from HEK[pTet-NL1-endo] cells can be regulated in a dose-dependent manner by Dox administration *in vitro*. In our previous study, we showed a dose-dependent secretion of ACTH from encapsulated Neuro2A-POMC cells implanted *in vivo* in the CSF of rats,

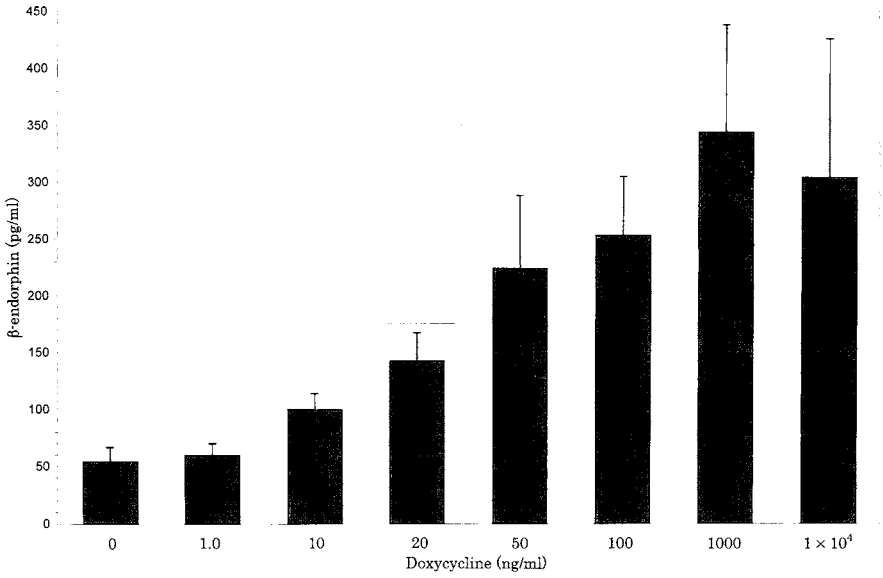


FIG. 1. Induction of β-endorphin secretion from HEK[pTet-NL1-endo] cells by administration of Dox. HEK[pTet-NL1-endo] cells (1.0×10^6 cells) were incubated in the presence of Dox at the indicated concentrations for 24 h, and the amounts of β-endorphin secreted from the cells into the medium were measured. Mean and standard deviation (SD) were calculated for each group ($n = 4$). The significance of differences in the concentration of β-endorphin among Dox dose groups was assessed using an analysis of variance (ANOVA) model that included Dox dose as independent variable ($P < 0.0001$). Further, variations due to linear contrast was significant ($P < 0.0001$) and positive linear trend of the concentration of β-endorphin with respect to Dox dose was suggested

upon administration of Dox to host peritoneum space [12]. Thus it can be envisaged that HEK[pTet-NL1-endo] cells, encapsulated and transplanted in the CSF of host animals, would secrete β-endorphin according to the various amounts of administered Dox. We are planning the test of this system in capsulated transplant in CSF space of monkey. This system can be adapted to many cell types by transfecting a plasmid expressing rtTA gene together with pTet-NL1-endo or its derivatives. As long as furin is active in the targeted cells, mammalian cell lines secreting any selected peptide could be established.

References

1. Rosenberg MB, Friedmann T, Robertson RC, et al (1988) Grafting genetically modified cells to the damaged brain: Restorative effects of NGF expression. Science 242:1575–1578
2. Shingo T, Date I, Yoshida H, et al (2002) Neuroprotective and restorative effects of intrastriatal grafting of encapsulated GDNF-producing cells in a rat model of Parkinson's disease. J Neurosci Res 69:946–954

3. Zurn AD, Henry H, Schluep M, et al (2000) Evaluation of an intrathecal immune response in amyotrophic lateral sclerosis patients implanted with encapsulated genetically engineered xenogeneic cells. Cell Transplant 9:471–478
4. Sagen J, Wang H, Tresco P, et al (1998) Transplants of immunologically isolated xenogeneic chromaffin cells provide a long-term source of pain-reducing neuroactive substances. J Neurosci 13:2415–2423
5. Saitoh Y, Taki T, Arita N, et al (1995) Analgesia induced by transplantation of encapsulated tumor cells secreting beta-endorphin. J Neurosurg 82:630–634
6. Braselmann S, Graninger P, Busslinger M (1993) A selective transcriptional induction system for mammalian cells based on Gal4-estrogen receptor fusion proteins. Proc Natl Acad Sci U.S.A. 90:1657–1661
7. Baim SB, Labow MA, Levine AJ, et al (1991) A chimeric mammalian transactivator based on the lac repressor that is regulated by temperature and isopropyl beta-D-thiogalactopyranoside. Proc Natl Acad Sci U.S.A. 88:5072–5076
8. Mayo KE, Warren R, Palmiter RD (1982) The mouse metallothionein-I gene is transcriptionally regulated by cadmium following transfection into human or mouse cells. Cell 29:99–108
9. Gossen M, Freundlieb S, Bender G, et al (1995) Transcriptional activation by tetracyclines in mammalian cells. Sicence 268:1766–1769
10. Noel G, Zollinger L, Laliberte F, et al (1989) Targeting and processing of pro-opiomelanocortin in neuronal cell lines. J Neurochem 52:1050–1057
11. Hagihara Y, Saitoh Y, Arita N, et al (1999) Long-term functional assessment of encapsulated cells transfected with Tet-On system. Cell Transplant 8:431–434
12. Saitoh Y, Eguchi Y, Hagihara Y, et al (1998) Dose-dependent doxycycline-mediated adrenocorticotropic hormone secretion from encapsulated Tet-On proopiomelanocortin Neuro2A cells in the subarachnoid space. Hum Gene Ther 9:997–1002
13. Ghaddar G, Ruchon AF, Carpentier M, et al (2000) Molecular cloning and biochemical characterization of a new mouse testis soluble-zinc-metallopeptidase of the neprilysin family. Biochem J 347:419–429
14. Saitoh Y, Eguchi Y, Nakahira R, et al (2004) Controlled secretion of β-endorphin from human embryonic kidney cells carrying a Tet-on-β-endorphin fusion gene. Brain Res Mol Brain Res 121:151–155
15. Gossen M, Bujard H (1992) Tight control of gene expression in mammalian cells by tetracycline-responsive promoters. Proc Natl Acad Sci U.S.A. 89:5547–5551

Human Gene Therapy for Malignant Gliomas

Toshihiko Wakabayashi[1,2], Jun Yoshida[1,2], Masaaki Mizuno[3], Masazumi Fujii[1], Yasukazu Kajita[1], Norimoto Nakahara[1], and Hisashi Hatano[1]

Summary. Clinical trial of gene therapy for malignant brain tumors has started on retroviral or adenoviral vectors to deliver suicide genes such as herpes simplex virus-thymidine kinase (HSV-tk) gene, which renders them sensitive to ganciclovir. However, there still remain numerous problems to overcome, such as the high immunogenicity and toxicity of viral vectors. To improve these problems, we investigated the transfer efficiency of interferon-beta gene via cationic liposomes, and has been found the remarkable antitumor effectiveness to induce regression of experimental glioma through the reasonable gene expression. Based upon these fundamental data, we performed a pilot clinical trial of safety and effectiveness of this interferon-beta gene therapy in five patients with malignant glioma. Transgene expression and antitumor activity were detected in four patients. Two patients showed a partial response (>50% tumor reduction) and two others had stable disease 10 weeks after beginning therapy. This study suggests the feasibility and safety of interferon-beta gene therapy, which may become an important minimal invasive treatment option for patients with malignant glioma.

Key word. gene therapy, glioma, interferon, liposome, clinical trial

1 Introduction

In the recent years, the prognosis of brain tumor patients has dramatically improved due to recent advances in neurosurgical operative procedures, which are included microneurosurgical techniques, development of intraoperative computer-assisted neuronavigation system (like as Neuronavigator), functional mapping, and neuro-

Departments of [1] Neurosurgery and [3] Human Gene Therapy, Nagoya University, Postgraduate School of Medicine, and [2] Center for Genetic and Regenerative Medicine, Nagoya University, School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan

monitoring system during operative procedure. Furthermore, development of neuroendoscopic surgery, intravascular surgery and radiosurgery are also assisted the improvement of survival and/or functional prognostic rate of brain tumor patients. According to a report by the Committee of Brain Tumor Registry of Japan, the ten year survival rate of patients with benign brain tumors (meningioma, neurinoma and pituitary adenoma) is more than 95%. In contrast, patients with glioma (which constitute 33% of primary brain tumor cases) still have a poor prognosis, especially in the case of malignant, which is included anaplastic astrocytoma and glioblastoma. This poor prognosis is related to the fact that malignant glioma cells aggressively infiltrate into normal brain tissues, making total removal of the tumor impossible. The median survival time of glioblastoma patients is less than two years, despite multimodality treatment with extensive surgical resection and adjuvant therapies using radiotherapy, chemotherapy, immunotherapy, hyperthermia and so on. In order to overcome this formidable neoplasm, the effectiveness of molecular biology using gene therapy has been investigated since 1992 in U.S.A. and 2000 in Japan. In this paper, molecular genetic studies and current state of gene therapy for brain tumors is described.

2 Clinical Trial of Gene Therapy

The clinical trial of human gene therapy was started in the United States in 1990 for immunodeficiency disease with a defective adenosine deaminase (ADA) gene using with patient's own gene-corrected T lymphocytes. Since this successful treatment, a variety of human gene therapy protocols have occurred worldwide. According to the worldwide gene therapy, more than 4,500 patients are enrolled in more than 250 different kinds of gene therapy protocols until now. Target diseases for this therapy has been expanding from congenital metabolic disorders to encompass acquired life-threatening diseases such as cancer, and at present, cancer is by far the most popular protocol. Nowadays, even chronic benign diseases are also expected to be a focus of this therapy.

As for the techniques for this therapy, until now, three different approaches are proposed. (1) Genes of disease interest are delivered into patients cells in order to produce a therapeutic protein; (2) Amplified tumor suppressor gene by insertion of modified plasmid or suppressed abnormal genes by antisense RNA or ribozyme and (3) Abnormal gene is replaced to normal genes by homologous recombination and repaired genomic DNA.

The vectors for gene transfer are classified into viral and non-viral. In the former, retrovirus vectors have been studied most extensively and hence are most commonly used for clinical application. However, the retrovirus vector has a limitation because it requires that target cells be dividing to achieve gene delivery and is rapidly inactivated in the blood. Thus most clinical applications of the retrovirus vector involve a complex ex vivo procedure whereby patients cells are removed and the gene is delivered in vitro. Another type of viral vector is derived from the adenovirus and adeno-associated virus (AAV). The adenovirus vector is capable of efficiently delivering a gene to several dividing and non-dividing cells. However, adenovirus genes express proteins that trigger an immune response. This immune response is believed to limit

the length of time that gene expression can be maintained in the target cell. AAV vectors are derived from AAV, a common non pathogenic human parvovirus. They may offer several potential advantages including efficient delivery of genes to both dividing and non-dividing target cells, potential site-specific integration of chromosome 19 and the absence of viral genes that may be responsible for causing an undesirable immune response. On the contrary, a limitation in the development of clinical application for AAV vectors has been the lack of an efficient production method.

On the other hand, non-viral vectors, especially DNA/liposomes are known to be much safer because they are non-infectious and non-immunogenic. Liposomes, artificially generated lipid vesicles that can entrap genes within their aqueous compartment or in the lipid bilayer, have been regarded as a useful gene delivery system. Nowadays, cationic liposomes-mediated gene transfer has been widely used in the field of gene therapy studies. By now, so many experimental groups have explored more efficient and less toxic cationic liposome compositions using different cationic lipids. And we have also developed novel cationic liposome with high transfection efficiency and low cytotoxicity which permit their use for in vivo gene transfer. Our liposomes are multilamellar vesicles (MLV) prepared by a simple procedure with N-(a-trimethyl ammonioacetyl)-didodecyl-D-glutamate chloride (TMAG), dilauroyl phosphatidylcholine (DLPC) and dioleoyl phophatidylethanolamine (DOPE) in a molar ratio of 1:2:2. In our experiments, the proportion of glioma cells that expressed the transfered DNA sequences and the absolute levels of expression obtained were markedly higher when the DNA/liposomes were used, compared to the levels, achieved with the other kind of DNA/liposomes.

3 Malignant Brain Tumor as A Target for Gene Therapy

Astrocytic gliomas are the most frequent human brain tumors. They are classified into four grades (astrocytoma as a agrade I-II, anaplastic astrocytoma as a grade III, and glioblastoma multiforme as a grade IV) on the basis of histopathological parameters. Malignant gliomas, which is included anaplastic astrocytoma and glioblastoma, in general, infiltrates aggressively into the surrounding normal brain tissue. That is the main reason why total resection of malignant gliomas by surgery is impossible, although recent advances in microsurgical technique are remarkable. Postoperative adjuvant therapy such as radiation, chemotherapy, immunotherapy, is applied to all patients with malignant gliomas. These adjuvant therapies sometime will help to prolong survival. However, none of these methods are curative, and the median survival time for malignant glioma patients which is less than 2 years at present.

Nevertheless, this malignant glioma has important features make it an excellent candidate for gene therapy. The brain is a closed cavity separated from the general circulation system by the blood-brain barrier, and it has been noted to be an immunologically privileged site with no lymphatic system. Furthermore, the glioma arising from a glia is a localized tumor in the central nervous system (CNS) with no extra-CNS metastasis.

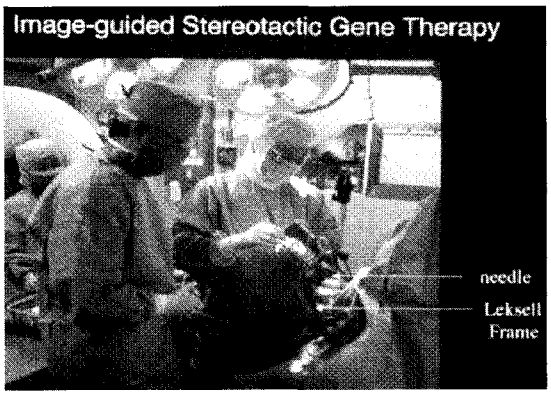


FIG. 1. A operative scene of gene therapy for brain tumors by stereotactic procedure

4 Fundamental Study of Gene Therapy for Malignant Brain Tumors

Until now, several kinds of gene therapy has been applied for malignant brain tumors. Mainly, (a) suicide gene therapy using the herpes simplex thymidine kinase (HSV-tk) gene and ganciclovir (GCV) and (b) immune gene therapy using cytokine genes, has been performed for malignant brain tumors.

In the case of suicide gene therapy, a team of the National Institute of health in the US (NIH) developed this remarkable new form of treatment.

With respect to immune gene therapy, we transfected human glioma cells with a plasmid vector containing the HuIFN-β gene (pSV2IFN-β) by means of our novel TMAG cationic liposome, and found that HuIFN-β produced in the cells had a much stronger inhibitory effect on the growth of the tumor cells than exogenously added HuIFN-β. Our results suggest that the mechanism causing the growth-inhibitory effect of transfection-induced HuIFN-β is different from the exogenous one. The former process is thought to be cytocidal to the transfected glioma cells, which can be ascribed to HuIFN-β production in the cells transfected with its gene by the process of apoptosis [3]. It has also been demonstrated that the transfected cells have the potential to inhibit growth or express cytotoxicity toward adjacent nontransfected glioma cells by means of local immune effect. In vivo experiments using transplanted human glioma growing in the brain of nude mice clearly showed that HuIFN-β was expressed in the solid tumor and that growth of the brain tumor was inhibited by intratumoral injection of cationic liposomes with entrapped pSV2IFN-β [2].

5 Clinical Application of Gene Therapy with Human Interferon β Gene Using Cationic Liposome

After confirmation of the suitability of the candidate of gene therapy by human gene therapy advisory board, the patient was operated to remove the recurrent tumor as much as possible, and after confirmation of pathological diagnosis of tumor recurrence, followed by stereotactic injection of the gene drug (Fig. 1). Gene therapy was

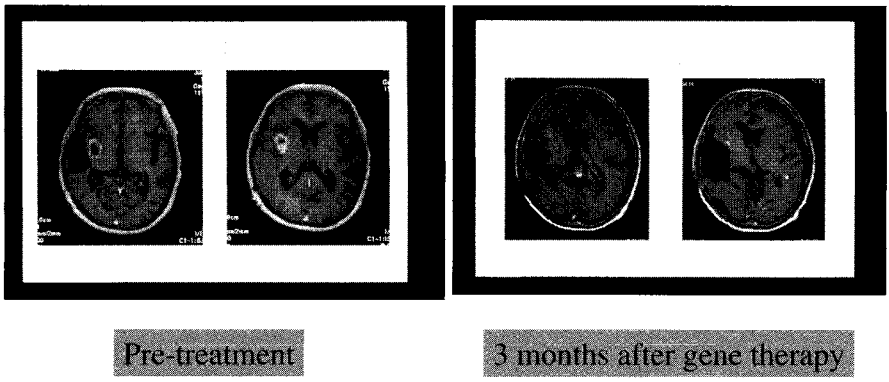


FIG. 2. Illustrative case. 64 y/o female, recurrent anaplastic astrocytoma at right temporal lobe. After gene therapy, remarkbale decrease in enhanced lesion was observed

performed at least four times during 1–2 week interval for one patient. After treatment, the patient was followed up by MRI almost every month and evaluated the effcicacy of the treatment during the careful observation for the safety of this therapy.

So far five patients was treated by this method. After gene therapy, at least two patients were shown the reduction of the tumor enhanced size on MRI and evaluated as a partial response (Fig. 2). Another two cases also were shown stable on MRI for a while and evaluated as a stable disease. All five patients didn't show any trouble more than third grade on NCI-CTC induced by gene therapy. [1]

These results suggest that the feasibility and safety of interferon-β gene therapy, which may become an important treatment option for patients with malignant brain tumors.

References

1. Yoshida J, Mizuno M, Fujii M, et al (2004) Humna gene therapy for malignant gliomas (glioblastoma multiforme and anaplastic astrocytoma) by in vivo transduction with human interferon beta gene using cationic liposome. Hum Gene Ther 15:77–86
2. Yoshida J, Mizuno M, Wakabayashi T (2004) Interferon-beta gene therapy for cancer: Basic research to clinical application. Cancer Sci 95:858–865
3. Mizuno M, Yoshida J, Sugita K, et al (1990) Growth inhibition of glioma cells transfected with the human β-interferon gene by liposomes coupled with a monoclonal antibody. Cancer Res 50:7826–7829

Neuronal Restoration of Memory Disturbances and Neuroprotection for Fall in Vegetation after Cardiac Arrest

NARIYUKI HAYASHI

Summary. There was no answer about how to prevent the fall in vegetation and memory disturbances following severe brain damage. Our recent clinical studies demonstrated that selective radical damage of dopamine A10 central nervous system are major causes of these memory and emotional dysfunction. The failure for control of excess release of cerebral dopamine and glutamate, non adequate initial management for the hemoglobin dysfunction by hypothalamus pituitary adrenal axis stress reaction, insulin resisted hyperglycemia, brain thermo-pooling phenomenon, and systemic circulatory-metabolic changes are considered as mechanism of fall in persistent vegetation. The early control of brain tissue temperature about 32–34°C, control of hemoglobin functions, adequate administration of oxygen and glucose in injured neurons, control of hypo-albuminemia are very useful for prevent of memory and emotional disturbances in brain resuscitation. As an indicator for diagnosis of reversibility from persistent vegetative state, response of oral muscle by facial touching, elevation of CSF dopamine/prolactin ratio by emotional stimulation, and increasing CSF neurotransmitters was very useful. In this paper, the evaluation scoring of persistent vegetative state is opened. The new concept of brain hypothermia treatment was considered to be effective for prevention of memory disturbances, recovery of vegetation and CPR non-response cardiac arrested patients.

Key words. brain hypothermia, dopamine, free radicals, scoring of vegetative state, cardiac arrest

1 Introduction

The understanding of mechanism of memory and emotional disturbances is one of the big issues in human life science. In our recent clinical studies, the mechanism of fall in vegetation, memory disturbances, and emotional retardation, have been demonstrated and much developed in clinical results for cardiac arrested patients [1–4]. We need more multiple viewpoint researches. In this paper, the mechanism of decline in vegetative state and memory disturbances, diagnosis of the reversibility of

Advanced Research Institute of Science and Humanities, Nihon University, 6F Ichigaya Tokyu Building, 4-2-1 Kudan-Kita, Tokyo 102-0073, Japan

the vegetative state, the scoring of persistent vegetation, management of neuronal dysfunction regarding emotion, memory, cognition, and behavior, and the clinical results of cardiac arrested patients are in focused.

2 The Mechanism of Decline in Vegetative State and Memory Disturbances

In all of previous clinical reports on effectiveness of pharmacological treatment for the vegetate state, memory and aphasia were associated with the replacement of dopamine [5–7]. All of these report suggested a close inter-relationships between the dopamine A10 central nervous system (hippocampus, hypothalamus, frontal cortex, accumbency nucleus, caudate nucleus, and amygdale nucleus) and the vegetative state [1–4,8]. The mechanism of the dopamine A10 nervous system comprises delicate motor and emotional memory function such as emotion, feeling of love, memory, thought, understanding, expression of anger, and volition (Fig. 1) [4]. Therefore, damage of dopamine A10 system could disturbs the memory and emotion, subsequently lead to a vegetative state or mental retardation [1–4] since the A10 central nervous system plays an important role these functions. The mechanism of selective damage of dopamine A10 nervous system could be explained as follow. Baker AJ et al [9] demonstrated that dopamine release occurs with deduction of DOPAC in ischemic brain of the rabbit. The extracellularly released dopamine from the injured dopamine nervous system, react with oxygen to produce hydrogen peroxide and quinine [10]. The hydrogen peroxide then changes to neurotoxic OH^- radicals [10]. The release dopamine from injured neurons causes selective radical damage to the dopamine nervous system in the brain (Fig. 1) [3,4]. The high incidence of simultaneous localized low density of the amygdale nucleus (77%) and hippocampus (88%) in persistent vegetation indirectly supports this mechanism of decline in the vegetative state (Fig. 2) [4].

3 Diagnosis of the Reversibility of the Vegetative State

The emotional stimulation by live music therapy could release the dopamine from hypothalamus and also suppress the pituitary function. This physiological reaction could be monitored by increasing of CSF dopamine and reducing CSF [4]. No observation of an increase in the CSF dopamine/prolactin ratio suggests poor functioning of the hypothalamus dopamine A10 nervous system. We monitored the changes of CSF dopamine/prolactin ratio for one month after live music therapy in 6 cases of persistent vegetative state patients. Increasing of CSF dopamine/prolactin ratio >1.0 was very useful in diagnosing the responsiveness of dopamine A10 nervous system [3,4]. The reversibility of vegetate state was diagnosed by simultaneous increasing of CSF dopamine/prolactin ratio and the cortical neuronal responsive marker, CSF norepinephrin and dopamine, by music stimulation [4]. This clinical evidence suggest that the dopamine A10 nervous system is a major part of the no need outer stimulation consciousness and is a very important management target for prevention of vegetative state in severe brain-injured patients [2–4].

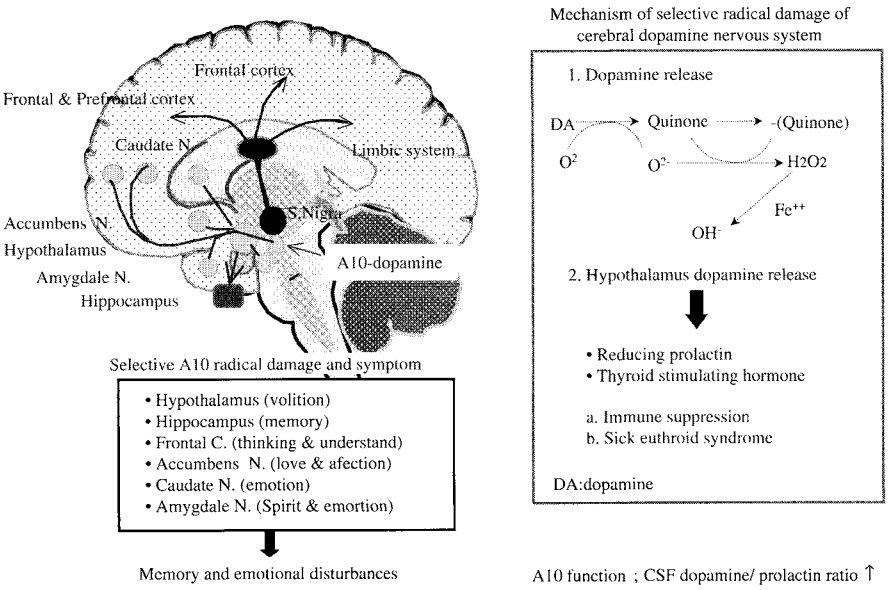


FIG. 1. The selective radical damage of dopamine A10 nervous system and immune suppression after severe brain damage. The responsiveness of cerebral dopamine A10 nerve system is evaluated with increasing of CSF dopamine/prolactin ratio

4 The Scoring of Persistent Vegetation

Persistent vegetation means the damage to self-consciousness that mainly consists of three major brain function, the dopamine A10 nervous system that integrated with limbic system and brain cortex functions. Our clinical studies suggested that response of emotional muscle around mouth and eyes by touching, increasing of CSF dopamine/prolactin ratio by treatment, and localized low density of hippocampus and amygdale nucleus on computed tomography (CT) (Fig. 2) are good indicators for evaluating the functioning of dopamine A10 nervous system [4]. However, brain cortex function is also necessary for maintaining of self-consciousness. I have contrived a 0–10 grading persistent vegetation evaluation score (PVES) card as shown on Table 1. Patients who have less than 1–2 points will find it very difficult to make a recovery from persistent vegetation; however, those scoring more than 8 points can progress much easily to recovery from a vegetate state. The prognosis of those who score 3–7 points patients is variable, depending on the original disease, extend of brain damage, complications of shock, age, gender, with or without brain hypothermia treatment, acuteness of brain damage, and starting time of treatment. This PVES-card is new idea for evaluating the grading of vegetative state, which hopefully can be used as a successful aid to clinical treatment in the future.

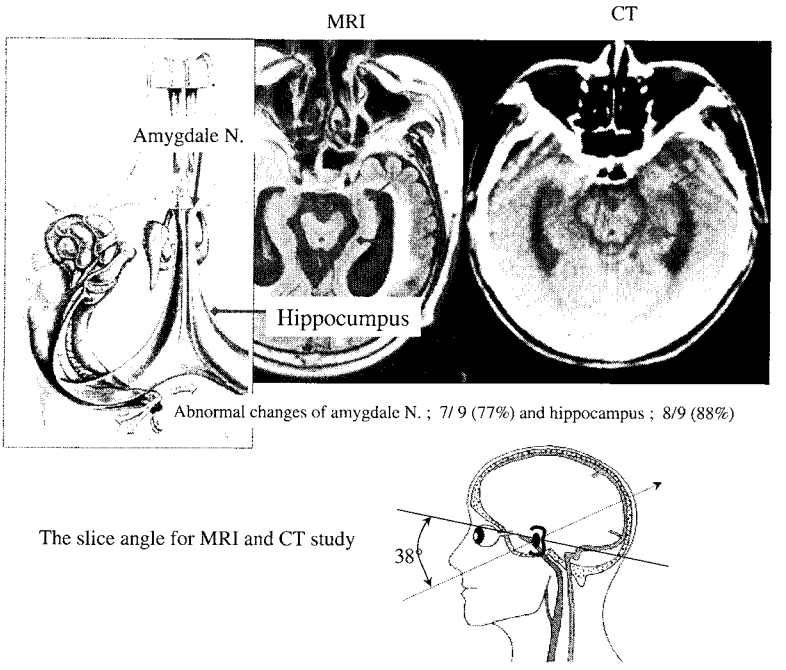


FIG. 2. The selective damage of hippocampus and amygdale nucleus in persistent vegetative state

TABLE 1. Persistent vegetative state evaluation score (PVES)

	Point			Score
	0	1	2	
Face muscle response by touch stimulation	O & J mouth	Around mouth	Around eyes	F 0–2
CT-picture	Hippocampus & amygdale both low	Hippocampus or amygdale low	Hippocampus & amygdale both no low	C 0–2
SEP N20	No response	Unilateral brain response	Bilateral brain responses	S 0–2
CSF dopamine/ prolactin ratio	<0.5	0.5–1.5	>1.5	D 0–2
CSF epinephrine	<5 ng/ml	5–10 ng/ml	>10 ng/ml	E 0–2

Example recording: F2, C1, S1, D1, E2.
Total score: 7.

5 Management of Neuronal Dysfunction Regarding Emotion, Memory and Behavior

5.1 Early Stage

The simple management for selective radical attack to the dopamine nervous system is prevention of dopamine release and control of NO radicals in acute stage. The early induction of brain hypothermia at 32–34°C is useful for prevent of dopamine release [2,3]. Pharmacological treatment, with metoclopramide also prevent the dopamine release from hypothalamus. Administration of radical scavengers such as serum albumin is another approach for prevent of selective damage of dopamine A10 nervous system at the acute stage [2–4]. As an additional phenomenon, release of brain tissue dopamine suppresses the release of prolactin and thyroid hormones [11]. To prevent of secondary immune dysfunction and sick euthroid syndrome as an additional complication of dopamine release, replacement of prolactin and thyroid hormone is important at acute stage [2–4].

5.2 Late Stage

At the post hypothermia late stage, the severe cases can't make a recovery of consciousness at all. The replacement of cerebral dopamine, the combination of pharmacological treatment such as Leodopa (300–400 mg/day), Amantadine (100–200 mg × 3/day) or Parodel (2.5–20 mg/day), and administration of estrogen (Estraderm TTS 1 seat/day) is effective. The median nerve intermittent electrical stimulation (20 s-on, 50 s-off, 10–20 mA, 30 pulses/s, duration time 300 mm/s) are also effective [2–4].

5.3 Chronic Stage

Emotion, memory, cognition, and behavior is consisted by many part of brain function. Therefore, the management of these complicated neuronal dysfunction is differs from the management of focal neuronal signs such as hemiparesis, visual disturbances and hearing disturbances.

(1) Mechanism of memory, cognition, and behavior disturbances: The memory, cognition, and behavior are highly associated with the Papez circle [12], which consists of the circuit of the hippocampus, cingulate gyrus, fornix, anterior thalamus, and mamillary nucleus. This circuit is also connected to the dopamine A10 nervous. Much information throughout the visual system, auditory system and sensory system is initially brought into the hippocampus [11,13,14]. This information is kept as a short memory and is check against the past memory in the cortex, and then the integrated information is translated into the Papez circuit and dopamine A10 nervous system [12]. The human memory, cognition, and behavior are decided and established throughout this information mechanism. Damage to memory, cognition, and behavior is produced by diffuse brain injury, severe brain hypoxia, and severe brain ischemia, including the Papez circuit [12].
(2) Management of emotion, memory, cognition, and behavior: The management of complicated neuronal dysfunction, which includes emotion, memory, cognition,

and behavior, are summarized as follows [4]. Neuronal environment care management: Maintaining the cerebral perfusion pressure, CBF, microcirculation and normal ICP are important with control of systemic circulation. Maintain of neuronal homeostasis: Enough oxygen delivery, prevent of anemia, maintained of hemoglobin function and oxygen delivery, prevent of hyperglycemia, and normal control of serum phosphate, magnesium and serum glucose [2–4]. Activation of injured neuronal function: Combination of dopamine replacement therapy and thyroid hormone replacement therapy. This neuron-hormonal replacement therapy is very effective in increasing nervous tension for rehabilitation and human communications. The combination of dopamine replacement therapy is described at before [2–4].

6 Clinical Results of Cardiac-arrested Patients

The clinical results of cardiac arrested patients in our medical center without brain hypothermia treatment show good recovery in only 6 of 187 (3.2%), and mortality in 166 of 187 (88.8%). The remaining 8% comprised 2.7% mild disability, 1.1% severe disability, and 4.3% vegetate state. These clinical results were unsuccessful in that they had poor outcome. Neuronal restoration therapy using percutaneous cardiopulmonary support system (PCPS) under the brain hypothermia treatment opened excellent clinical results [4]. Figure 3 shows the care plan for cerebral resuscitation after cardiac arrest [4]. Little difference in our clinical result was observed between the two groups. Group B had a slightly lower incidence of decline in vegetative state [4]. In-group A, normal or minimal disability outcomes were recorded in 13 of 29 (44.8%).

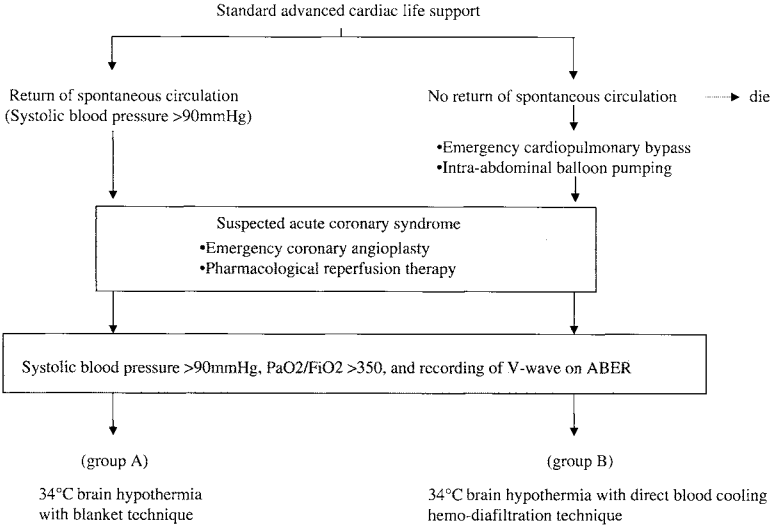


FIG. 3. The care plan for cerebral resuscitation after cardiac arrest. *ABER*, auditory brain stem evoked potential

The incidence of severe disability, vegetate state, and death were recorded in 1 of 29 (3.4%), 9 of 29 (31.1%), and 6 of 29 (20.7%), respectively. In-group B, good recovery or minimal disability was recorded in 12 of 23 (52.2%), slightly better than group A. Moderate disability, vegetate state, and death were recorded in 1 of 23 (4.3%), 2 of 23 (8.7%), and 8 of 23 (34.8%), respectively. The total clinical result of brain hypothermia for cardiac arrest with entry criteria was 48.1% good recovery, 1.9% moderate disability, 1.9 % severe disability, 21.2% of vegetate state, and 26.9% of death. Brain hypothermia treatment for post resuscitation of cardiac arrest was considered to be effective [4,14].

References

1. Hayashi N (1997) Prevention of vegetation after severe head trauma and stroke by combination therapy of cerebral hypothermia and activation of immune-dopaminergic nervous system. Soc Treat Coma 6:133–145
2. Hayashi N (200) The clinical issue and effectiveness of brain hypothermia treatment fore severe brain injured patients. In: Hayashi N (ed.) Brain hypothermia. Springer-Verlag, Tokyo, pp 121–151
3. Hayashi N (2004) Clinical management of brain hypothermia. In: Hayashi N, Dietrich DW (eds) Brain hypothermia treatment. Springer-Verlag, Tokyo, pp 37–325
4. Hayashi N, Mori T, Kinoshita K, et al (2004) Persistent vegetation means unconsiousness? How to manage vegetation and memory disturbances following severe brain damage. In: Hayashi N, Bullock R, Dietrich DW, et al (eds) Hypothermia for acute brain damage. Springer-Verlag, Tokyo, pp 327–342
5. Crisman LM, Childs A, Wilcox RE, et al (1988) The effect of bromocriptine on speech dysfunction in patients with diffuse brain injury. Clin Neuropharmacol 11:462–466
6. Gualtieri CT, Chandler M, Coons TB, et al (1989) Review. Amantadine: A new clinical profile for traumatic brain injury. Clin Neuropharmacol 12:258–270
7. Haig AJ, Ruess LM (1990) Recovery from vegetative state of six months' duration associated with Sinemet (levodopa/carbidopa). Arch Phys Med Rehabil 71:1081–1083
8. Hayashi N (1997) Combination therapy of cerebral hypothermia, pharmacological activation of the dopamine system, and hormonal replacement in severely brain damaged patients. J Jpn Intensive Care Med 4:191–197
9. Baker AJ, Zornow MH, Scheller MS, et al (1991) Changes in extrascellular concentrations of glutamate, asparate, glycine, dopamine, serotonin, and dopamine metabolites after transient global ischemia in the rat. J Neurochem 57:1370–1379
10. Silvka A, Coben G (1985) Hydroxyl radical attack on dopamine. J Biol Chem 260:15466–15472
11. Creutz LM, Kritzer MF (2002) Estrogen receptor-beta immunoreactivity in the midbrain of adult rats: Regional, subregional, and cellular localization in the A10, A9, and A8 dopamine cell groups. J Comp Neurol 446:288–300
12. Papez JW (1937) A proposed mechanism of emotion. Arch Nuerol Psych 38:725–743
13. Livingston KE, Escobar A (1971) Anatomical bias of the limbic system concept: A proposed reorientation. Arch Neurol 24:17–21
14. Nagao K, Hayashi N, Kanmatuse K, et al (2000) Cardiopulmonary cerebral resuscitation using emergency cardiopulmonary bypass, coronary perfusion therapy and mild hypothermia in patients with cardiac arrest outside the hospital. J Am Coll Cardiol 36:776–783

Neuroprotection and Repair by Using Adult-derived Neural Stem Cell Grafting for Neurological Disorders

Isao Date, Tetsuro Shingo, Takao Yasuhara, Kazuya Takahashi, and Kenichiro Muraoka

Summary. It has long been held that central nervous system is not able to regenerate after injury, but this concept has recently been changing due to the emergence of new findings from neuroscience research. Cell grafting, gene transfer and neurotrophic factor administration into the brain and spinal cord are examples of methods employed to investigate mechanisms of protection and repair. In the development of stem cell biology, neural stem cells existing in the adult brain have been shown to have the capacity to give rise to the three cell lineages in the central nervous system and can be a good donor source for neuronal protection and repair. Adult-derived neural stem cells have three merits as donor cells; (1) autologous transplantation can be applied, (2) no or less risk of tumor formation and (3) can avoid ethical issues related to fetus derived neural stem cells. This review will summarize the history and perspectives of neural transplantation for neurological disorders from the viewpoint of adult-derived neural stem cells with particular attention to Parkinson's disease and cerebral ischemia.

Key words. neuroprotection, neural stem cell, adult-derived, neural transplantation, autologous grafting

1 Introduction

At present, restorative medicine and gene therapy are considered central to the practice of medicine in the 21st century, and neurological disorders such as Parkinson's disease are important therapeutic targets. Actual clinical application of cell transplantation has been performed in Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, intractable cancer pain and cerebral ischemia. In the case of Parkinson's disease, the first cell transplant clinical trial was performed to treat this disease, the highest number of basic research findings have been published, and

Department of Neurological Surgery, Okayama University, 2-5-1 Shikata-cho, Okayama 700-8558, Japan

numerous new approaches to regenerative therapy have been applied. In cerebral ischemia, intracerebral grafting of hNT cells has already been applied in the clinical setting. Because the grafting of stem cells from various sources had already been clinically applied to myocardial infarction or arteriosclerosis obliterans of the lower limbs, many studies aimed at clinical applications to cerebral ischemia using stem cells are underway. In this review, the current status and future perspectives of neural transplantation with a focus on adult derived neural stem cell grafting will be summarized.

2 Transplantation of Dopaminergic Neurons Derived from Adult Neural Stem Cells in Parkinson's Disease

Neural stem cells have certain established features of self-renewal, proliferation and multipotency, and these features have come to be well-known in fetal and neonatal brains. It has been possible to culture neural stem cells selectively by the "neurosphere method" developed by Reynolds and Weiss [1] using growth factors such as EGF and FGF-2; several studies using this methodology have shown the presence of neural stem cells not only in the fetal brain but also in the adult brain. It has also been demonstrated that neural stem cells can develop into neurons, astrocytes and oligodendrocytes by the simple removal of these trophic factors from the culture media. Because it has been become possible to increase the number of neural stem cells in an almost unlimited fashion by this culture method, these cells have drawn attention as a new source of donor cells for neural transplantation.

Neural stem cells in the adult brain have been discovered in the subventricular zone (SVZ) of the lateral, third and fourth ventricles and in the subgranular cell layer in the dentate gyrus of the hippocampus [2,3]. Neural stem cells in the SVZ of the lateral ventricle migrate into the olfactory bulb via a rostral migratory stream (RMS) and give rise to new neurons in the granular cell and periglomerular cell layers. Although most of the new neurons develop into GABA neurons, some develop into dopaminergic neurons. This suggests that the neural stem cells derived from the SVZ can be used as transplant donor cells for Parkinson's disease.

When dopaminergic neurons derived from neural stem cells are to be used as the cell therapy donor cells for Parkinson's disease instead of fetal nigral dopaminergic neurons, the following conditions below must be met: (1) stable production of dopamine, (2) parkisonian symptoms of the animal models have been documented as alleviated when transplanted into the animal brain, (3) at least 100,000 grafted dopaminergic neurons in the human striatum survive in the long-term and (4) neural circuit reconstruction is induced by the grafted neurons and the grafted neurons integrate into the host striatum [4]. Studies are underway to ascertain whether neural stem cells meet these criteria. It has been reported that functional recovery and differentiation into dopaminergic neurons have been confirmed when human fetus derived neural stem cells were grafted into parkinsonian model animals [5]. However, the number of surviving dopaminergic neurons in the host striatum to date has been insufficient. One of the problems is that midbrain derived neural stem cells in primary culture can differentiate into dopaminergic neurons, but when cell passage is performed, very few cells differentiate into dopaminergic neurons but rather most differentiate into GABA neurons. It may be excessively difficult to maintain the character

of neural stem cells with the potential to differentiate into dopaminergic neurons under the culture conditions reported thus far. Hence, several methods have been investigated for obtaining a greater number of dopaminergic neurons from the fetal midbrain-derived neural stem cells and neural progenitor cells: (1) differentiation inducing factors such as lowered oxygen [6], ascorbic acid and cAMP [7], IL-1b, IL-11, LIF, and GDNF [8], (2) clonal neural progenitor cells with the capacity to differentiate into dopaminergic neurons [9] and (3) the overexpression of Nurr 1, a gene which induces differentiation into dopaminergic neurons [10,11]. A method of forming a cluster of graft cells by means of a three dimentional culture procedure has been reported to enhance the survival of transplanted cells [12].

The authors have paid attention to the fact that neural stem cells in the SVZ migrate into the olfactory bulb, and a portion of these cells differentiate into dopaminergic neurons in adult mice. Neural stem cells removed from the SVZ were passaged several times with EGF, and these cells were differentiated with a TH inducing cocktail under EGF and serum free conditions. Approximately 40% of the cells differentiated into dopaminergic neurons [13]. When these dopaminergic neurons derived from adult SVZ were grafted into the striatum of parkinsonian model animals, the grafted dopaminergic neurons survived in the host brain and functional recovery of the host animal was observed. Using similar methods, differentitation into dopaminergic neurons from neural stem cells in the SVZ of adult monkeys has also proved to be successful. These results suggest the possibility of autologous transplantation of neural stem cell derived dopaminergic neurons in parkinsonian patients.

3 Application of Adult-derived Neural Stem Cells for the Treatment of Cerebral Ischemia

Adult-derived neural stem cells secrete many types of neurotrophic factors and cytokines (Table 1). The authors have paid special attention to erythropoietin (EPO), which is an important factor for differentiation from blood stem cells to red blood cells. When the brain receives certain stimulation, astrocytes and radial glia initiated

TABLE 1. Neurotrophic factors and cytokines secreted from neural stem cells

BDNF	Galectin	Sonic hedgehog
BMPs	GDNF	TGFs
CNTF	IGFs	VEGF
EGF	NT-3,4/5	WNTs
EPO	NGF	
FGFs	PDGF	

BDNF, brain-derived neurotrophic factor; BMPs, bone morphogenetic proteins; CNTF, ciliary neurotrophic factor; EGF, epidermal growth factor; EPO, erythropoietin; FGFs, fibroblast growth factors; IGFs, insulin-like growth factors; NT, neurotrophin; NGF, nerve growth factor; PDGF, platelet-derived growth factor; TGFs, transforming growth factors; VEGF, vascular endothelial growth factor.

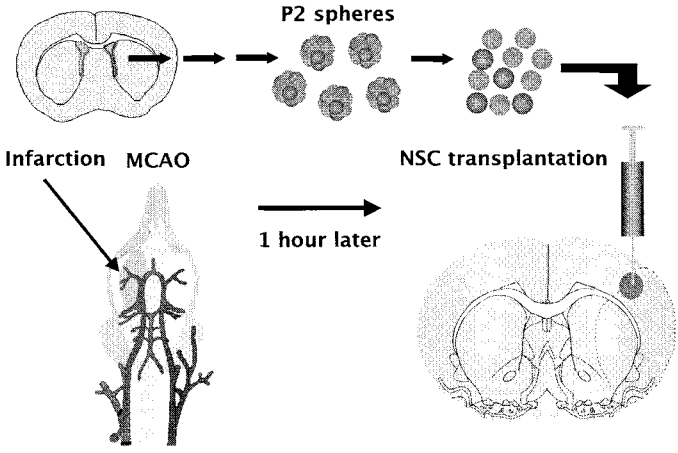


FIG. 1. Adult-derived neural stem cell grafting for cerebral ischemia. Neural stem cells obtained from the SVZ of adult rat were cultured and transplanted into the cerebral cortex of the host rat whose ipsilateral middle cerebral artery was transiently occluded

to secreted EPO and recently neuroprotective effect of EPO for cerebral ischemia has been reported [14]. The authors also have shown that EPO plays an important role when neural stem cells differentiate into neurons [15]. EPO production from the adult-derived neural stem cells is similar to that from embryo-derived neural stem cells after first passage.

The authors transplanted adult-derived neural stem cells into the transient cerebral ischemia model of rat and evaluated whether adult-derived neural stem cells have effect of neural protection (Fig. 1). Neural stem cells obtained from the SVZ of adult rat were cultured with EGF for one month with passages and transplanted into the rat cerebral cortex. Ipsilateral middle cerebral artery was transiently occluded and the size of infarction was measured for one months using MRI. The animals receiving adult-derived neural stem cells showed significant reduction of infarction size compared with the one receiving vehicle (Fig. 2). Although most of the grafted cells differentiated into glia, some of the cells differentiated into neurons. Some of the cells migrated through corpus callosum and moved to ventral cerebrum. These data indicate the neuroprotective effect of adult-derived neural stem cells for cerebral ischemia and suggest a new therapeutic approach for cerebral ischemia.

4 Autotransplantation of Neural Stem Cells into the Brain

Techniques have been established to culture neural stem cells from adult rodents such that it is now possible to induce them to proliferate in an almost unlimited manner if at least one neural stem cell can be dissociated as the starting cell. This suggests that autotransplantation of neural stem cell might be viable if the tissue in the subventricular zone could be removed stereotactically. The authors successfully extracted

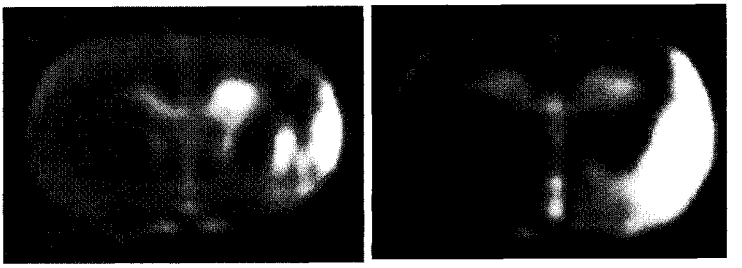


FIG. 2. T2 weighted image of the ischemic rat receiving cell grafting (day 28). The host rat receiving adult-derived neural stem cells (left) had smaller volume of infarction (high intensity area) than control rat (right)

neural stem cells from the subventricular zone of adult rats in a stereotactic fashion, and cultured them while also preserving the surrounding tissue. Although approximately 10,000 cells could be obtained by this method, only about 50 neurospheres were formed among these. However, it proved possible to expand the number to 1,000,000 by passaging the cells three times under proliferative conditions. Also, it was important that the ratio of differentiation into neurons from neural stem cells of adult origin was not statistically different from those of fetal origin. This suggests that the necessary number of cells for neural transplantation could be obtained from extracted autologous neural stem cells for a period of one month, and the same result can be expected as that obtained with donor cells from fetus derived neural stem cells.

Using the above mentioned TH-inducing cocktail, the authors investigated whether stereotactically removed autologous neural stem cells could be differentiated into dopaminergic neurons. We confirmed that proliferated neural stem cells could be differentiated into neurons in the presence of EGF, and approximately 40% of these neurons were TH positive. HPLC analyses confirmed dopamine secretion from these neurons. This result suggest that autologous neural stem cells are candidate donor cells for cell therapy in Parkinson's disease.

We then investigated whether adult derived autologous neural stem cells are able to survive in the host brain when transplanted, and whether these stem cells differentiate into neurons. We transplanted adult derived autologous neural stem cells into the dentate gyrus of adult rat hippocampus, where active neurogenesis has been observed. The number of surviving cells in the area of the hippocampal granular or subgranular cell layer was significantly higher when autologous neural stem cells were used as donors as compared with allogeneic or fetus derived neural stem cells. Histological analyses revealed a lesser degree of observable reactive astrocytes and proliferatine microglia around the grafted area when autologous neural stem cells were used as the donors. The number of neurons differentiated from the grafted neural stem cells detected in the area of transplantation was significantly higher when autologous neural stem cells were used, although most of the surviving cells were undifferentiated cells. These preliminary data suggest the potential usefulness of autologous neural stem cells as donor cells. Studies are ongoing regarding the administration of neurotrophic factors and cytokines as well as the induction of certain genes in order to enhance the diffentiation of grafted neural stem cells into neurons.

We also intend to perform transplantation of dopaminergic neurons derived from autologous neural stem cells using the TH cocktail into animal models of Parkinson's disease.

Regarding the future clinical application of autologous neural stem cell transplantation, a system of stable dissociation and the culturing of adult derived neural stem cells will need to be established. Since Palmer et al reported the cell culture of progenitor cells from the human brain after death [16], several methods have been investigated to enable culture of neural stem cells of adult origin, but a stable methodology has not yet been fully established. A number of issues need to be resolved, for example, (1) less invasive removal of neural stem cells from adult brain, (2) sufficient expansion of neural stem cells as to allow effective neural transplantation and (3) analysis of the characteristics of the adult derived neural stem cells, etc. Although these issues remain important and will have to be resolved, it nonetheless appears certain that autologous neural stem cell grafting will continue to be a useful method of cell therapy, not least because it allows the avoidance of certain immumological and ethical problems which are the bane of other approaches.

References

1. Reynolds BA, Weiss S (1992) Generation of neurons and astrocytes from isolated cells of the adult mammalian central nervous system. Science 255:1707–1710
2. Weiss S, Dunne C, Hewson J, et al (1996) Multipotent CNS stem cells are present in the adult mammalian spinal cord and ventricular neuroaxis. J Neurosci 16:7599–7609
3. Palmer TD, Takahashi J, Gage FH (1997) The adult rat hippocampus contains primordial neural stem cells. Mol Cell Neurosci 8:389–404
4. Hagell P, Brundin P (2001) Cell survival and clinical outcome following intrastriatal transplantation in Parkinson disease. J Neuropathol Exp Neurol 60:741–752
5. Svendsen CN, Caldwell MA, Shen J, et al (1997) Long-term survival of human central nervous system progenitor cells transplanted into a rat model of Parkinson's disease. Exp Neurol 148:135–146
6. Studer L, Csete M, Lee SH, et al (2000) Enhanced proliferation, survival, and dopaminergic differentiation of CNS precursors in lowered oxygen. J Neurosci 20:7377–7383
7. Sanchez-Pernaute R, Studer L, Bankiewicz KS, et al (2001) In vitro generation and transplantation of precursorderived human dopamine neurons. J Neurosci Res 65:284–288
8. Storch A, Paul G, Csete M, et al (2001) Long-term proliferation and dopaminergic differentiation of human mesencephalic neural precursor cells. Exp Neurol 170:317–325
9. Carvey PM, Ling ZD, Sortwell CE, et al (2001) A clonal line of mesencephalic progenitor cells converted to dopamine neurons by hematopoietic cytokines: A source of cells for transplantation in Parkinson's disease. Exp Neurol 171:98–108
10. Wagner J, Akerud P, Castro DS, et al (1999) Induction of a midbrain dopaminergic phenotype in Nurr1-overexpressing neural stem cells by type 1 astrocytes. Nat Biotechnol 17:653–659
11. Kim JY, Koh HC, Lee JY, et al (2003) Dopaminergic neuronal differentiation from rat embryonic neural precursors by Nurr1 overexpression. J Neurochem 85:1443–1454
12. Studer L, Tabar V, McKay RD (1998) Transplantation of expanded mesencephalic precursors leads to recovery in parkinsonian rats. Nat Neurosci 1:290–295
13. Shingo T, Weiss S (2000) Robust induction of tyrosine hydroxylase in embryonic and adult striatal neural stem cell-derived neurons in defined media and the absence of gene transfer. Soc Neurosci Abstr 26:830

14. Sakanaka M, Wen TD, Matsuda S, et al (1998) In vivo evidence that erythropoietin protects neurons from ischemic damage. Proc Natl Acad Sci U.S.A. 95:4635–4640
15. Shingo T, Sorokan ST, Shimazaki T, et al (2001) Erythropoietin regulates the in vivo and in vitro production of neuronal progenitors by mammalian forebrain neural stem cells. J Neurosci 21:9733–9743
16. Palmer TD, Schwartz PH, Taupin P, et al (2001) Cell culture. Progenitor cells from human brain after death. Nature 411:42–43

Diaphragm Pacing with a Spinal Cord Stimulator

TAKAOMI TAIRA and TOMOKATSU HORI

Summary

Background: Diaphragm pacing with electrical stimulation of the phrenic nerve is an established treatment for central hypoventilation syndrome. The device, however, is not readily available. We used the spinal cord stimulator for pain control for phrenic nerve stimulation.

Methods: We implanted a stimulator for spinal cord stimulation (Itrel 3 or X-trel, Medtronic, MN) in 6 patients with chronic hypoventilation because of brainstem or high cervical cord dysfunction of various origins. The stimulation electrode was placed along the right phrenic nerve in the neck, and the device was implanted in the anterior chest. We used the cyclic mode, and set the parameters at 1 s ramp up, 2 s on, 3 s off. The pulse width and the frequency were set at 150 μs and 21 Hz, respectively. The amplitude of the output was adjusted to obtain sufficient tidal volume and to maintain PaCO2 at around 40 mmHg.

Results: During the follow-up period up to three years, stable and sufficient ventilation were observed in all patients without complications. One patient with sleep apnea syndrome used the device only at night and became free from a respirator. Three patients who had been completely respirator-dependent became ambulatory during the daytime.

Conclusion: Though longer follow-up is necessary, diaphragm pacing with the spinal cord stimulator is feasible for a treatment of central hypoventilation syndrome.

Key words. central hypoventilation, diaphragm pacing, spinal cord stimulator

Chronic hypoventilation because of dysfunction of the brainstem or the high cervical spinal cord poses a serious medicosocial problem. Patients with such hypoventilation are usually managed with the use of artificial ventilators. However, chronic use

Department of Neurosurgery, Neurological Institute, Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan

TABLE 1. List of the patients

Patient no.	Age (year)	Cause of hypoventilation	Condition	Hypoventilation duration (month)
1	58	SAH due to vertebral artery aneurysm, intraoperative rupture	Sleep apnea, respirator only at night	6
2	58	Operative complication of jugular foramen neurinoma	Totally dependent on respirator	4
3	63	Spontaneous brainstem hemorrhage, no operation	Totally dependent on respirator	8
4	55	Spontaneous brainstem hemorrhage, no operation	Totally dependent on respirator	3
5	34	AAD surgery complication	Totally dependent bil implant	9
6	42	Gun shot/C1–2 cord injury	Totally dependent	14

of positive pressure ventilation is not physiological, easily causes infections, and restricts the patient's activities. It has been known for a long time that diaphragm pacing with an implanted electric device to stimulate the phrenic nerve is a reasonable solution for such patients [1–5]. Almost all the patients with diaphragm pacing so far have been using a device specifically made for this purpose by Avery Laboratories Inc. (Commack, NY). Because this device is not readily available in our country, we applied a stimulator for spinal cord stimulation or deep brain stimulation for pain control to electrical stimulation of the phrenic nerves to pace the diaphragm. The aim of this study is to prove the feasibility of diaphragm pacing with electrical stimulators originally made for pain relief. Patients and Methods From March 2000 to September 2004, we performed diaphragm pacing using a stimulator for spinal cord stimulation in 6 patients with chronic hypoventilation because of brainstem dysfunction who were on a ventilator. After detailed discussion with the patient's family and the patient, if possible, we obtained written informed consent. There were one man and three women ranging in age from 34 to 63 years (mean age, 51.6 years). These patients were reviewed, retrospectively. Table 1 summarizes the profile of these patients with regard to age, gender, and the cause, and duration of hypoventilation.

1 Determination of Stimulation Parameters

Before applying the stimulator in the clinical setting, the waveform of the output from the stimulation device was checked. According to the reports on optimal stimulation parameters for diaphragm pacing [4,5], we tested the various types of stimulators for spinal cord stimulation or deep brain stimulation. We tried the Itrel 2 (Medtronic, model 7426), originally manufactured for deep brain stimulation for movement disorders, the Itrel 3 (Medtronic, model 7425) for pain control, the radiofrequency-driven X-trel system (Medtronic, model 3470) for pain control, and the Matrix dual output system (Medtronic, model 3272). Among them, the Itrel 3 and the X-trel system had a function of cyclic output suitable for artificial respiration. A dummy resistor of 1,000 ohm was connected to the output and the waveforms were checked with an

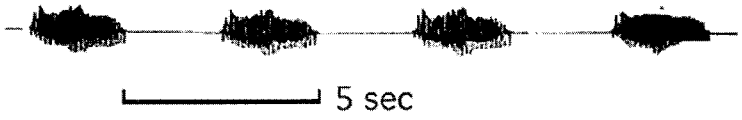


FIG. 1. Output of spinal cord stimulator adjusted for phrenic pacing

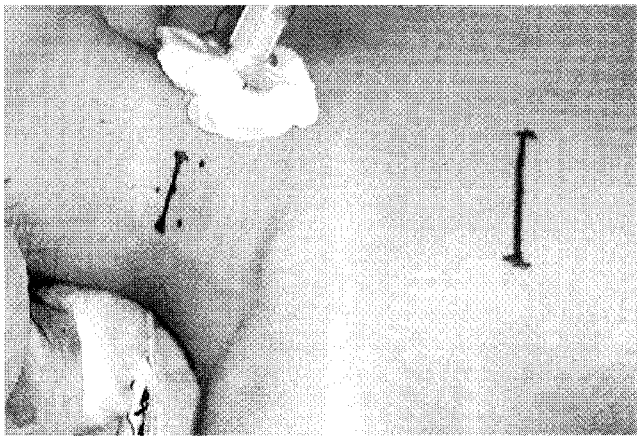


FIG. 2. Skin incision

oscilloscope (Fig. 1). In this study, we decided to set the parameters at the cyclic mode, 2 s on with 1 s ramp up, and 3 s off, resulting in the respiratory rate being 12 per minute. According to the stimulation parameters of the device specifically manufactured for phrenic pacing (Avery Laboratories Inc.) [4,5], we set the pulse width and the frequency at 150 μs and 21 Hz, respectively.

2 Operative Technique

All patients were operated on under general anesthesia in the supine position with the head rotated to the left side. Muscle relaxant was not used to monitor intraoperative contraction of the diaphragm. We implanted the stimulation electrode to the right phrenic nerve, because the right lung has larger volume. A linear horizontal skin incision 4 cm in length was made at 4 cm rostral to the right clavicle, crossing the posterior border of the sternocleidomastoid muscle (Fig. 2). The subcutaneous tissue was dissected and the sternocleidomastoid muscle was retracted medially. After exposure of the anterior scalene muscle, the phrenic nerve was identified over the scalene muscle with monopolar electrical stimulation (5 or 50 Hz, 1 ms pulse width, 0.5–2 volts). Under an operative microscope, the nerve sheath was carefully exposed for about 1 cm in length, but we did not dissect between the nerve and the scalene muscle. A quadripolar lead-type electrode for deep brain stimulation (Medtronic, model 3387-28) was placed along the nerve and fixed with two sutures to the surrounding connective tissues (Fig. 3). With another skin incision in the anterior upper chest, the stimulation

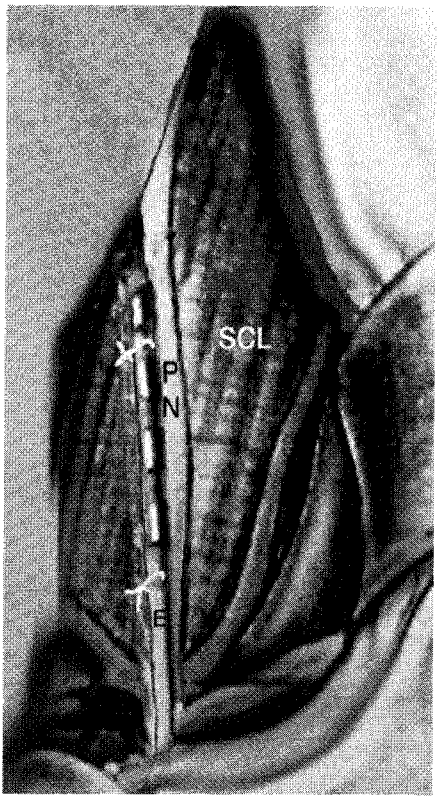


FIG. 3. Stimulation electrode placed adjacent to the phrenic nerve

device was placed subcutaneously, and the lead was tunneled and connected to the lead electrode. At first, we set the output of the stimulator as in the studies in vitro. The amplitude of the output was adjusted so that the tidal volume was approximately 500 ml. The most proximal contact of the quadripolar electrode to the stimulator was used as negative and the most distal contact as positive. Two contacts between them were set as "off." After the operation, the carbon dioxide pressure of the exhalation and the arterial oxygen saturation in the fingertip were monitored until the values became stable. The carbon dioxide pressure in the end tidal air was adjusted to about 40 mmHg by changing the output voltage of the stimulator. We did not change the respiratory rate except in Case 1. To avoid fatigue of the phrenic nerve and diaphragm [1,4,5], we used the stimulator only in the daytime in patients who required artificial ventilation for 24 h. For a patient with sleep apnea but sufficient ventilation in the awake state, we trained her to switch on the device before going to bed.

3 Discussion

Artificial ventilation with phrenic nerve stimulation has a long history [2,4,5]. Because the device became commercially available (Avery Laboratories Inc.), it has been

implanted in many patients [1–3]. The efficacy and problems of this treatment with the device system have been documented in detail [1–5]. The reason we started using the spinal cord stimulator for diaphragm pacing is that the device specifically made for phrenic nerve stimulation is not readily available in our country. The Ministry of Health and Welfare in Japan has not approved the device by Avery Laboratories as a medical device. If we were to import the device personally, the cost would be high and most patients could not afford it. Of course, the cost of the device is not reimbursed by medical insurance in Japan. We think this situation is true in many other countries. We have to solve such domestic problems, but in the meantime our patients cannot wait for approval. In contrast to the lack of availability of the device for diaphragm pacing, the spinal cord stimulator is commonly used and covered by insurance in Japan, when it is used for pain control. Thus the hurdles are not high in the use of spinal cord stimulators. The longevity of the battery in the Itrel 3 stimulator is about 5 years when used for pain control with continuous output. Compared with the ordinary stimulation parameters for pain control (e.g., 50 Hz, 200 μsec pulse width, 3 volts, and 8 h continuous use per day), the output parameters for diaphragm pacing in the present cases resulted in only about 12.5% in terms of consumption of electricity. Simple calculation with such information indicates that the battery longevity of the Itrel 3 when used for phrenic nerve stimulation is theoretically 8 times longer than in spinal cord stimulation for pain control. We used an electrode for deep brain stimulation and placed it along the phrenic nerve. Ideally, the stimulation electrode should be atraumatic to the nerve and securely fixed, like the spiral shaped electrode for vagal nerve stimulation for intractable epilepsy. Because the electrical current may spread to the surrounding tissues with such an electrode, we had worried that local muscle contraction or electrical evoked sensation might cause a problem for the patients. However, we did not experience such a problem. The use of a spinal stimulator for diaphragm pacing has no warranty from the manufacturer. An emergency backup system is not established. Therefore, we performed the procedure solely on our own responsibility. Although long-term follow-up is necessary, we conclude that the spinal cord stimulator system can be used for phrenic nerve stimulation for diaphragm pacing as a compromise.

References

1. Chervin RD, Guilleminault C (1997) Diaphragm pacing for respiratory insufficiency. J Clin Neurophysiol 14:369–377
2. Elefteriades JA, Quin JA (1998) Diaphragm pacing. Chest Surg Clin N Am 8:331–357
3. Garrido-Garcia H, Mazaira Alvarez J, Martin Escribano P, et al (1998) Treatment of chronic ventilatory failure using a diaphragmatic pacemaker. Spinal Cord 36:310–314
4. Glenn WW, Holcomb WG, Shaw RK, et al (1976) Long-term ventilatory support by diaphragm pacing in quadriplegia. Ann Surg 183:566–577
5. Glenn WW, Phelps ML (1985) Diaphragm pacing by electrical stimulation of the phrenic nerve. Neurosurgery 17:974–984

Intraoperative Monitoring of the Corticospinal MEP (D-wave) in Brain Tumor Surgery

TAKAMITSU YAMAMOTO[1,2], YOICHI KATAYAMA[1,2], TAKAFUMI NAGAOKA[1], KAZUTAKA KOBAYASHI[1,2], and CHIKASHI FUKAYA[1,2]

Summary. We employed the corticospinal motor evoked potential (D-wave) as a monitoring index of motor function to perform maximal resection of brain tumors located around the motor cortex. Thirty-seven patients were included in the present study. For monitoring of the D-wave, operations were performed under general anesthesia with muscle relaxant and completely controlled ventilation. No special arrangements for anesthesia were required. Monitoring of the D-wave enabled the function of the corticospinal tract to be evaluated selectively. Postoperative persistent motor disturbance remained in 6 patients who exhibited an over 30% decrease in amplitude of the D-wave during tumor resection. A less than 30% decrease could guarantee a postoperatively preserved motor function which included a period of transient motor disturbance with subsequent complete recovery. Intraoperative monitoring of the D-wave is suitable for open cranial surgery with general anesthesia. It is useful for detection of the primary motor cortex and for achieving maximal resection of brain tumors located around the motor cortex.

Key words. motor cortex, motor evoked potential, corticospinal tract

The recently reported procedure of awake surgery [1,2], which employs local anesthesia and intravenous injection of propofol and lenitive drugs, can guarantee a preserved motor function in cases of tumor resection around the motor cortex and subcortical motor tract. It is well known that the disturbed motor function which is caused by injury of the supplementary motor cortex [3] or premotor cortex [4] can undergo complete recovery within several weeks. Awake surgery is a very useful method and can secure a preserved motor function if the motor function is intact

[1] Department of Neurological Surgery and [2] Division of Applied System Neuroscience, Nihon University School of Medicine, 30 Ohyaguchi Kamimachi, Itabashi-ku, Tokyo 173-8610, Japan

during the operation; however, it is unable to achieve maximal tumor resection which involves transient motor disturbance and subsequent functional recovery.

We have reported in humans that the corticospinal motor evoked potential (corticospinal MEP) in response to direct stimulation of the motor cortex can be recorded from the epidural space of the spinal cord [5–7].The corticospinal MEP response consists of an initial D-wave and a later sequence of volleys termed I-waves [8,9]. The D-wave reflects impulses arising from direct activation of the axons of corticospinal tract (CTS) neurons, whereas the I-waves reflect impulses arising from indirect activation of the CTS neurons via synaptic activity, and the corticospinal MEP is recorded only when the primary motor cortex is stimulated [8,9].

Monitoring of muscle responses to direct motor cortex stimulation is also a useful procedure. However, care needs to be exercised concerning the anesthesia, use of muscle relaxant, α-motoneurons, and intraoperative convulsions. Unlike muscle responses to motor cortex stimulation [10,11], the D-wave of the corticospinal MEP is resistant to surgical doses of anesthetics and is unaffected by muscle relaxants [5], apart from changes to the excitability of spinal motoneurons [12]. It is easily recorded in every case of preserved motor function, and is activated by low frequency single stimulation with no fear of causing general convulsions or after-discharges during the monitoring of motor function [5–7].

We employed the corticospinal MEP for detection of the primary motor cortex and for securing maximal resection of brain tumors located around the motor cortex, and compared the changes in corticospinal MEP (D-wave) with the postoperative motor disturbance including the subsequent functional recovery.

1 Methods

For the present study, we enlisted 37 consecutive patients who had brain tumors around the motor cortex and showed no obvious motor disturbance before the operation. Patients exhibiting motor weakness before surgery were not included in this study. The subjects comprised patients with glioma located at the premotor cortex (15 cases), supplementary motor cortex (4 cases), primary motor cortex (12 cases), and primary sensory cortex (6 cases). In the present study, reference to the premotor cortex means that the tumor was located in the frontal lobe and anterior to the precentral sulcus except the most medial aspect, and also that the precental sulcus was found to be intact on magnetic resonance imaging (MRI). The supplementary motor cortex means the same as the premotor cortex except that the tumor was located at the most medial aspect of the frontal lobe anterior to the leg region of the primary motor cortex. The primary motor cortex means that the tumor invaded even partly into the precentral gyrus of the hand, trunk, thigh, or foot area from the anterior or posterior direction. The primary sensory cortex means that the tumor was located in the parietal lobe invading into the postcentral gyrus, and that the central sulcus was intact on MRI. All patients gave informed consent for intraoperative monitoring of the corticospinal MEP to be performed. The present study was approved by the Committee for Clinical Trials and Research in Humans of our university and by the Japanese Ministry of Health and Welfare as part of an advanced medical care program.

A flexible 4-channel, platinum wire electrode (Quad, Medtronic Co. 3487A) was inserted into the epidural space of the cervical vertebrae, usually at the C3–C4 level, on the day before surgery. Each subject was placed in the abdominal prone position, and an 18-gauge Touhy needle included in the electrode package was inserted into the midline epidural space at the cervical and thoracic junction under X-ray control. The spinal epidural space was confirmed from the change of resistance observed in practice with saline injection through the Touhy needle. The electrode was inserted into the epidural space with a stylet through the Touhy needle and advanced to the appropriate position under X-ray control. The stylet and Touhy needle were then removed, and the electrode was fixed with adhesive tape and a drape on the skin. The inserted wire electrode with four contact points, numbered 1 to 4 sequentially from the most rostral contact 1 to the most caudal contact 4, was used for bipolar recording between contacts 1 and 2, and between contacts 3 and 4 simultaneously, in response to stimulation of the motor cortex exposed during the surgery. Each contact of the recording electrode was 3 mm long, and the contacts were 6 mm apart from each other. The difference in peak latency of the D-wave, recorded between contacts 1 and 2 and between contacts 3 and 4, was employed constantly to calculate the conduction velocity of the D-wave. The scalp of the forehead was grounded.

During brain tumor resection, the motor cortex and other cortical areas were directly stimulated with a multicontact plate electrode (Unique-Medical Co., Japan). This device has four contact points and each plate electrode is 5 mm in diameter and spaced 5 mm apart. Each of the plate electrodes was embedded in thin and soft silicone material aiming to maintain good contact with the cerebral cortex. The response was evoked by bipolar stimulation with various pairs of electrodes. The interpolar distance for bipolar stimulation thus varied from 10 to 30 mm. The stimuli were applied as monophasic square wave pulses of 0.2–0.5 ms duration delivered at 2 Hz. Signals from the electrodes were fed into an amplifier with a bandpass range of 5 Hz to 5 kHz and averaged for 16–32 sweeps using SYNAX 2100 (NEC, Japan) or 7S12 (San-ei Inc., Japan). For the monitoring of the corticospinal MEP, all operations were carried out under general anesthesia with muscle relaxant and completely controlled ventilation. No special arrangements for anesthesia were required (Fig. 1).

2 Results

2.1 Identification of Primary Motor Cortex

Cranial openings were cut that were sufficient to expose the motor cortex and surrounding cortices from bone landmarks by means of a method usually employed for intracranial surgery. After opening the dura, the multicontact plate electrode was first placed on the cortical surface in a direction so that the longitudinal axis was parallel to the sagittal sinus and at 60 mm lateral from the midline. The four electrodes were numbered 1, 2, 3 and 4, respectively, beginning arbitrarily from one end to the other. In a typical case, the brain tumor was present in the frontal lobe with an intact precentral sulcus and precentral gyrus. The posterior border of the tumor was identified by intraoperative ultrasonography, and one pole of stimulation electrode No. 4 was placed on the middle frontal gyrus, just posterior to the tumor border. Electrode No.

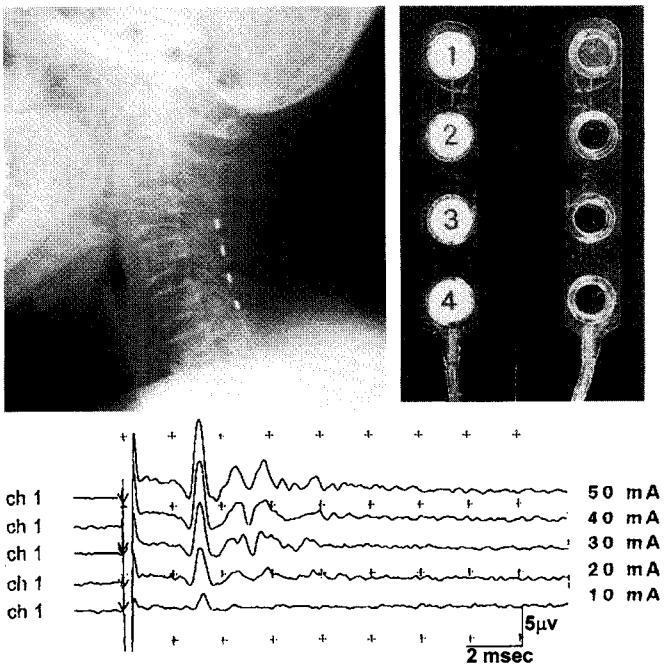


FIG. 1. Upper left: Radiograph showing a 4-channel wire electrode placed within the epidural space of the C3–C4 cervical spinal cord. Upper right: Multicontact plate electrode for direct cortical stimulation. The device has four contact points, and each plate electrode is 5 mm in diameter and spaced 5 mm apart. Lower: Cortico-spinal MEP recordings. The stimulation intensity was increased from 10 mA to 50 mA. (Time scale, 2 ms; amplitude, 5 μV)

3 was located on the anterior half of the precentral gyrus, electrode No. 2 on the posterior half of the precentral gyrus, and electrode No. 1 on the postcentral gyrus close to the central sulcus. The extents of cerebral cortex which could evoke the D-wave were examined by bipolar stimulation with various pairs of electrodes comparing the threshold of the D-wave. In this case, comparison of the threshold with various pairs of electrodes located side by side (10 mm distance) revealed that the threshold of the D-wave was lowest with bipolar stimulation between electrodes No. 1 and 2, and between electrodes No. 2 and 3, and when electrode No. 2 was used as the anode. In a similar manner, the threshold increased when electrode No. 3 or No. 1 was stimulated with the anode and electrode No. 2 with the cathode. The D-wave was not recorded with bipolar stimulation between electrodes No. 3 and 4 when electrode No. 4 was stimulated with the anode [7]. The cortical area which could evoke the D-wave was clearly separated from the surrounding cortices. If one electrode was placed on the posterior half of the precentral gyrus, the D-wave could be recorded even with 10 mm-distant bipolar cortical stimulation. In addition, when only one pole of the stimulation electrode was placed on the posterior half of the precentral gyrus, the amplitude was larger with anode rather than cathode stimulation [7].

2.2 D-wave Monitoring and Postoperative Motor Function

During intraoperative monitoring of the corticospinal MEP (D-wave) for tumor resection around the motor cortex, the longitudinal direction of the multicontact plate electrode was positioned parallel to the motor strip and just on the primary motor cortex. The location of the multicontact plate electrode was not altered once monitoring had been initiated. Since the multicontact plate electrode maintained good contact with the cortical surface, and was covered with a damp cotton sheet, no trouble was caused by movement of the stimulating electrode even during the tumor resection. The selection of an interpolar distance of 30 mm (between electrodes No. 1 and 4) was made because an interpolar distance of more than 10 mm clearly produced a D-wave with a high amplitude. During the operation, the D-wave was recorded constantly with good reproducibility. The average and standard deviation of the conduction velocity in the 37 cases, as calculated from the difference in peak latency of the D-wave over two recording sites (18 mm), was 62.1 ± 3.5 m/s. Neither convulsive seizures nor epileptic discharges on the patients' electroencephalograms were induced during the monitoring of the corticospinal MEP.

The pre- and postoperative motor function was evaluated by the muscle maneuver test (MMT), and the results of fine movements were excluded. In the 15 cases of glioma located at the premotor cortex, the amplitude of the D-wave decreased between 0 to 23% during the tumor resection. Eight of the 15 cases (53%) displayed transient motor disturbance, which underwent complete recovery within 2 weeks, while the other 7 cases showed no motor disturbance during the postoperative period. In the 4 cases of glioma located at the supplementary motor cortex, the amplitude of the D-wave decreased 5, 12, and 20% in 3 cases and exhibited no decrease in the other 1 case. All 4 cases demonstrated transient hemiparesis and aphasia, which also underwent complete recovery within 2 weeks. In the 12 cases of glioma invading into the precentral gyrus, the amplitude of the D-wave decreased 10 to 73%, and all 12 cases displayed hemiparesis or hemiplegia immediately after the operation. In 6 cases, which showed 10, 13, 17, 20, 25, and 38% decreases in amplitude of the D-wave, motor function recovered completely within 2 weeks. However, the other 6 cases with 31, 45, 55, 60, 65, and 73% decreases in amplitude of the D-wave demonstrated long-lasting motor disturbance without subsequent recovery. Despite the fact that all these 6 cases retained motor disturbance, they were able to walk by themselves because the retained motor disturbance was more apparent in the upper extremities as compared to the lower extremities: the MMT was 3 in the upper extremity and 4 in the lower extremity even in the case which showed the maximal reduction (73%) in amplitude of the D-wave. All 6 cases without permanent motor disturbance were ones where the tumor was invading into the primary motor cortex from the anterior border and not from the posterior border. In the 6 cases of glioma located at the primary sensory cortex, the D-wave did not change in 4 cases, while 2 cases showed decrease of 8 and 12%. None of these 6 cases revealed motor disturbance during the postoperative period.

Postoperative persistent motor disturbance appeared in 6 cases which exhibited an over 30% decrease in amplitude of the D-wave. Thirty other cases with a less than 30% decrease in amplitude of the D-wave and 1 case with a 38% decrease revealed no motor

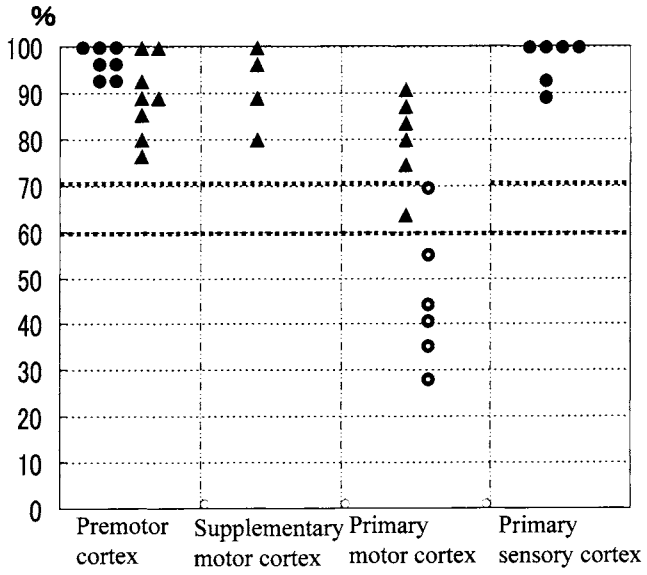


FIG. 2. Comparison between changes of D-wave amplitude and postoperative motor function. The amplitude of the D-wave recorded after tumor resection was divided by the amplitude recorded before tumor resection. 100% means no change in amplitude of the D-wave. Motor function was estimated by the MMT, and fine movements of the hand were excluded. ●: No motor disturbance appearing after tumor resection. ▲: Transient motor disturbance with complete recovery within 2 weeks. O: Permanent motor disturbance without recovery

disturbance or transient motor disturbance followed by complete recovery. These findings suggest that from a 30 to 40% decrease in the D-wave amplitude is critical for causing persistent motor disturbance, and that a less than 30% decrease can guarantee a postoperatively preserved motor function including transient motor disturbance with subsequent complete recovery except for fine movement disorders (Fig. 2).

3 Discussion

In order to prevent or reduce postoperative motor deficits in cases of brain tumors located around the motor cortex, several methods for the intraoperative monitoring of motor function have been introduced into routine practice [1,5,6,10,11]. The motor cortex can be stimulated directly during tumor resection in open cranial surgery [5–7]. In addition to awake surgery, the corticospinal MEPand muscle response to direct motor cortex stimulationcan be used for the monitoring of motor function. Each technique has certain advantages and disadvantages, and it is clear that no one technique in particular is superior for all cases of intraoperative monitoring. Monitoring of the muscle response to direct motor cortex stimulation is a clinically useful procedure, and Kombos et al [10] reported that a reduction in amplitude larger than

80% and a prolongation of latency more than 15% can be interpreted as intraoperative warning signs of risk of mechanical damage to the motor system. In comparison with the muscle response to direct motor cortex stimulation, the D-wave of the corticospinal MEP has advantages in the following respects [5–7]: (1) the D-wave is resistant to surgical doses of anesthetics and is unaffected by muscle relaxants, (2) the D-wave is not affected by changes in the excitability of spinal motoneurons, (3) the D-wave which can be recorded in this way is stable and accurate in all cases requiring intraoperative monitoring, and is suitable for deciding the critical level for functional recovery and (4) low frequency single stimulation is sufficient to evoke the D-wave, with no fear of causing general convulsions or after-discharges during the monitoring. Although intraoperative awake surgery can provide a guarantee of postoperative intact motor function, special efforts to cooperate with the anesthesiologists are required, and we sometimes experience severe brain edema (especially in cases of large brain tumors) and feel difficulty in operating through inter-hemispheric approaches without hyperventilation. Further, we usually find that apparently disturbed motor function during the period of the postoperative state undergoes complete recovery within several weeks after the tumor resection. Awake surgery is the best method for monitoring the function of fine movements, however, it is difficult with awake surgery to complete maximum tumor resections which lead to transient motor disturbance and subsequent complete recovery.

Corticospinal MEP monitoringhas disadvantages in that the recording electrode must be inserted into the cervical epidural space prior to the operation. Concerning this point, if the subjects are placed in the abdominal prone position, and the Touhy needle is inserted into the middle point under X-ray control, it is easy and safe to place the recording electrode in the cervical epidural space. Since 1986, we have already experienced over 200 cases without complications arising from the electrode insertion [5–7].

The calculated conduction velocity of the D-wave was within the range 56.3 to 64.3 m/s in the present study, which is similar to values obtained previously for the D-wave of corticospinal neurons of the cat and monkey reported previously [8,9]. This range of conduction velocity is consistent with the conduction velocity of fast corticospinal neurons. The D-wave follows double pulse stimulation with interstimulus intervals of more than 500 Hz, and the features of the D-wave suggest that this wave is a volley mediated by a simple fiber tract without intervening synapses [5]. Amassian et al [8] reported that the corticospinal D-wave has been inferred to result from activation of the cell bodies and/or axons of corticospinal neurons rather than apical dendrites arborizing in the superficial layer. Numerous experimental studies [5,7–9,13] have indicated that an anodal current, rather than a cathodal current, is suitable for activating deeply located initial segments or axons of corticospinal neurons from which the D-wave originates. Our results also demonstrated that the lowest threshold to evoke the D-wave was anodal stimulation of the posterior half of the precentral gyrus, and if one pole of the bipolar stimulating electrode was located on the posterior half of the precentral gyrus or anterior half of the precentral gyrus and stimulation was with the anode and not the cathode, a D-wave could be recorded even with an interpolar distance of 10 mm for cortical stimulation. A D-wave was not recorded with anodal stimulation of the premotor or supplementary motor cortex with an interpolar distance of 10 mm. Thus, an interpolar distance of 10 mm for cor-

tical stimulation provides practically useful information concerning the location of the primary motor cortex and its differentiation from the supplementary motor and premotor cortices.

Various reviews, clinical observations, and experimental studies on animals have indicated that the disturbed motor function caused by injury of the supplementary motor cortex [3,4,13] and premotor cortex [4] can undergo spontaneous recovery within several weeks. Zentner et al [3] reported that surgically induced supplementary motor cortex injury induced transient motor and speech disturbance with complete recovery, and the muscle response to direct motor cortex stimulation revealed no significant changes in potentials. The electromagnetically elicited MEP, examined postoperatively, was initially absent but recovered with improvement of motor function. We employed the corticospinal MEP for intraoperative monitoring of the motor function in brain tumor cases involving the supplementary motor cortex, premotor cortex, primary motor cortex, and primary sensory cortex, and concluded that if the decrease in amplitude of the D-wave was under 30%, postoperative motor disturbance was absent or transient with complete recovery except for fine movements. In our 37 cases, the critical point for eliciting persistent motor disturbance was a 30 to 40% decrease in amplitude of the D-wave. The reason why a persistent motor deficit does not appear with less than a 30% decrease in amplitude of the D-wave still remains uncertain. Further studies are needed to clarify the detailed mechanisms operating between the CTS neurons and motor function.

We also found that cases without permanent motor disturbance after resection of a tumor invading to the precentral gyrus were always from the anterior direction and not from the posterior direction, and the results of effective stimulation sites for D-wave activation also indicated the importance of the posterior half of the precentral gyrus for motor function. The corticospinal MEP is useful not only for cortical mapping but also for monitoring of the motor function which includes the subcortical motor tract. At first, when we began monitoring the corticospinal MEP for cortical tumor resection, the D-wave decreased over 30% in some cases. However, we then decided to stop tumor resection before the decrease in amplitude of the D-wave reached 30%, and have recently encountered no permanent motor deficit following tumor resection. The D-wave is resistant to anesthetics and muscle relaxants, and is suitable for cranial open surgery under usual general anesthesia. In our experience, the monitoring of the corticospinal MEP (D-wave) during tumor resection around the motor cortex represents a most reliable and useful tool for achieving maximal tumor resection, which gives rise to transient motor disturbance with subsequent functional recovery.

Acknowledgement. The present work was supported by grants from the Ministry of Education, Culture, Sports, Science, and Technology for the promotion of the industry-university collaboration at Nihon University.

References

1. Berger MS, Kincaid J, Ojemann GA, et al (1989) Brain mapping techniques to maximize resection, safety, and seizure control in children with brain tumors. Neurosurgery 25:786–792

2. Berger MS, Ojemann GA, Lettich E (1990) Neurophysiological monitoring during astrocytoma surgery. Neurosurg Clin N Am 1:65–80
3. Zentner J, Hufnagel A, Pechstein U, et al (1996) Functional results after resective procedures involving the supplementary motor area. J Neurosurg 85:542–549
4. Freund HJ (1984) Premotor area in man. Trends Neurosci 7:481–483
5. Katayama Y, Tsubokawa T, Maejima S, et al (1988) Corticospinal direct response in humans: Identification of the motor cortex during intracranial surgery under general anaesthesia. J Neurol Neurosurg Psychiatry 51:50–59
6. Tsubokawa T, Katayama Y, Yamamoto T (1995) Intraoperative monitoring of corticospinal and spinospinal MEPs. In: Dimitrijevic (ed.) Atlas of human spinal cord evoked potentials. Butterworth-Heineman, Boston, pp 85–96
7. Yamamoto T, Katayama Y, Nagaoka T, et al (2004) Intraoperative monitoring of thr corticospinal motor evoked potential (D-wave): Clinical index for postoperative motor function and functional recovery. Neurol Med Chir (Tokyo)
8. Amassian VE, Stewart M, Quirk GJ, et al (1987) Physiological basis of motor effects of transient stimulus to cerebral cortex. Neurosurgery 20:74–93
9. Patton HD, Amassian VE (1954) Single—and multiple-unit analysis of cortical stage of pyramidal tract activation. J Neurophysiol 17:345–363
10. Kombos T, Suess O, Ciklatekerlio O, et al (2001) Monitoring of intraoperative motor evoked potentials to increase the safety of surgery in and around the motor cortex. J Neurosurg 95:608–614
11. Taniguchi M, Cedzich C, Schram J (1996) Modification of cortical stimulation for motor evoked potentials under general anesthesia: Technical description. Neurosurgery 38:962–970
12. Jankowska E, Padel Y, Tanaka R (1975) Projection of pyramidal tract cells to alpha-motoneurons innervating hind-limb muscles in the monkey. J Physiol (Lond) 249:637–667
13. Gorman ALF (1966) Differential patterns of activation of the pyramidal system elicited by surface anodal and cathodal cortical stimulation. J Neurophysiol 29:547–564

Functional Neurosurgical Rehabilitation in Craniovertebral Junction Abnormality. An Exemplary Case Report

KLAUS R. H. VON WILD

Summary. Today, thanks to the tremendous progress in modern neurosurgery, intensive care treatment, CT, MRI, and PET diagnostic imaging techniques and multidisciplinary management of complications ever more patients survive from severe brain and spinal cord lesions, mainly secondary to trauma, tumours, vascular pathologies, and congenital malformations. Functional impairments after difficult and risky operative procedures or concomitant complications may also cause disturbances of sensory motor and mental-cognitive behavioural functioning that are assessed today according to the WHO-ICF criteria. Early postoperative Neurorehabilitation aims at functional recovery. It starts with the assessment of the impairments and the underlying pathophysiology by using all modern diagnostic tools. Its efficiency can be exemplary demonstrated in one patient who developed an acute Locked-in Syndrome after ventral decompression and dorsal fixation of a C0-C1 congenital malformation secondary to instability with local compression of the lower brain stem. Rehabilitation is a team approach for personal interaction and has to respect the patient's and the relative's needs and social-cultural background. The second look operation followed our algorithm for treatment of craniovertebral abnormalities. The postoperative course was uneventful and the patient regained consciousness. Being still on the ventilator the severe tetraparesis improved over time with aid of active nursing, neuropsychological, physical-, physio-, occupational- and speech/language therapies at the ICU. After four months (FIM better 30 points, ERBI above 50 points) he was transferred for long term rehabilitation. After two years he was fully reintegrated into social life and his job as an active soldier. This case report demonstrates the importance of individually tailored functional rehabilitation in neurosurgery that became a challenge for young neurosurgeons.

Professor of Neurosurgery, Medical Faculty, Westf. Wilhelms-University, Münster, NRW; Professor of Neurorehabilitation and Re-engineering of brain and spinal cord lesions, International neuroscience Institute, Hannover; Director kvw-neuroscience consulting GmbH, 32 Frauenburgstrasse, D-48155 Münster, Germany

Key words. functional rehabilitation in neurosurgery, algorithm for management of craniovertebral malformation, cervicomedullary compression, assessment of locked-in syndrome, WHO—ICF classification of functioning, spectrum of neurosurgical neurorehabilitation, holistic neurorehabilitation, outcome and quality of life

1 Objectives

Developmental and acquired craniovertebral junction abnormalities may become symptomatic secondary to chronic medullar and upper cervical cord compression or ischemia of neural tissue of the brain stem, medulla oblongata and pons. This can be secondary to an acute indirect impact in craniocerebral trauma and/or cervical spine injury [1]. Patients suffering from Locked in syndrome typically demonstrate symptoms and signs of alert wakefulness with paralysis of the body and inability to speak but are relatively cognitively intact [1,2] mainly due to vascular rather than traumatic consequences [3]. Altered level of consciousness, syncope, vertigo, and episodic hemi or tetraparesis present as neurological symptoms can be the consequence of vascular compromise after repetitive trauma to the vessels, for example, resulting from pathological hypermobility of an unstable atlantoaxial joint and permanent angulation or stretching of the feeding arteries [1–5]. Perilous is an unexpected sudden respiratory arrest secondary to local anterior and/or posterior compression of the cervicomedullary junction. This happened in a patient with typical craniocervical malformation C0-C1 after surgical decompression and fixation. Prognosis of impaired functioning depends on the underlying pathology and the time window for medical intervention. Clinical symptoms and signs due to ischemia, secondary to local compression of the arterial and venous blood supply, can be resolved either by a conservative treatment with immobilization or following surgical decompression by anterior and posterior approach, with stabilisation when necessary. The operative procedures have to be tailored for each patient according to the complete assessment of functional anatomy, pathophysiology, and radiological abnormalities. Functional rehabilitation, following operative procedures with fusion, however, is not specially mentioned in this context [1,6–9]. There are insufficient data in the literature regarding neurosurgical rehabilitation in the postoperative Locked-in-syndrome therefore it must be emphasised that in this rare and challenging clinical situation only attendant holistic rehabilitation can lead to the final and successful functional outcome.

1.1 Patient and Methods

K.O. 38 years old man, an active soldier in the army of Saudi Arabia for many years, sustained a blunt head injury when accidentally hit by a tank in November 2001. Following the injury there was increasing and finally a severe tetraparesis with a sensory impairment under C2. Plain roentgenograms, tomographic studies, and the computerized tomography of the craniovertebral junction revealed a complex abnormality with compression of the displaced cervicomedullary junction. The odontoid process extended more than one half of its length a the Chamberlain's line while the disc C1/C2 persisted. Subluxation of C0-C1 and narrowing of the foramen magnum increased

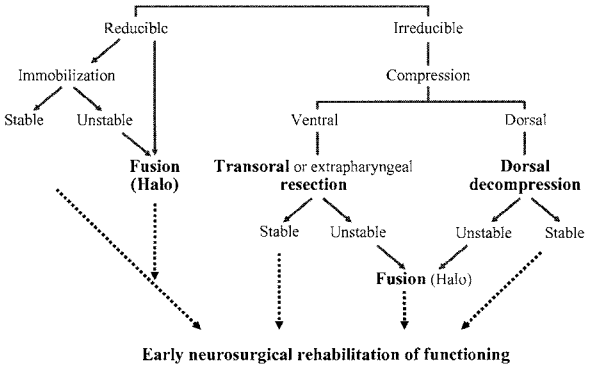


FIG. 1. Algorithm for medical treatment and early rehabilitation of impaired functioning after Van Gilder and Menzes

during flexion and extension X-ray investigation; there was a vertebral body bloc C2/C3 (Fig. 1).

The patients was seen by an orthopaedic surgeon, who is also a neurosurgeon and expert in craniovertebral procedures in Germany. After careful completion of the diagnosis the patient underwent surgery on December 28, 2001. Obvious congenital compression of the brain stem and instability C0-C1 required both the ventral and posterior approach. Therefore, as a first step, the upper part of the odontoid was removed by transoral approach which aimed at the decompression of the nervous structures for restoring the vascular supply and functions of the motor and sensory pathways. Subsequently, in the second step, dorsal stabilisation was performed with plates and rods using the Cervifix®-system and bone grafts which were attached to the occiput and facets. The operative procedures were uneventful. However, there was postoperative arrest of spontaneous breathing combined with an increasing tetraparesis. The patient was in the subsequent postoperative period left intubated and connected to the ventilator at the intensive care unit (ICU). CT and MRI control studies did not show blood clot or mass lesion in the operative field with instrumentation and bone graft in place. The neurological and cognitive signs and symptoms of an incomplete Locked-in syndrome fluctuated so that recurrent intubations and artificial ventilation were necessary to maintain oxygen saturation until the patient finally deteriorated again and became comatose and tetraplegic at the end of the second postoperative week. Following the consultation, the patient was referred for functional early neurorehabilitation to our department of Neurosurgery nearby the hospital of his primary surgery on January 18, 2002.

As usual neurosurgical rehabilitation started already in the intensive care unit (ICU) with careful assessment of the underlying pathophysiology of the impaired functioning. Following the immediate stabilization of the craniovertebral junction by extension with the aid of the Gardner Wells tongs and tracheotomy all electrophysiological, X-rays, CCT and MRI imaging diagnostic investigations were performed. The interdisciplinary team approach was carefully planned, including all the medical specialists and the rehabilitation personnel, taking into consideration the family and his Saudi Arabian background when defining the ultimate goal of holistic neurorehabilitation, the patient's reintegration into family, society and his reemployment. The

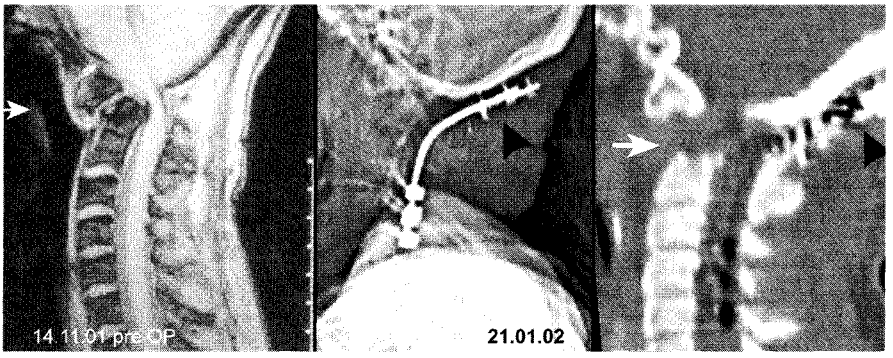


FIG. 2. Sagittal MRI, TSE T2, TR 3500, TE 120 preoperative (14. 11. 01) (left). Complex congenital abnormality of the craniovertebral junction (white arrow) with displacement and local (vascular?) compression of the lower brain stem and upper cervical cord due to bony narrowing of the surrounding space as cause of acute posttraumatic tetraparesis. Sagittal spiral CCT control postoperatively (right) shows the resection of the bone after ventral approach and the dorsal cranio-cervical fixation

clinical diagnose was Locked-in syndrome obviously due to vascular compression of the upper and lower brain stem because of postoperative, once more, instability at C0-C1, as it was demonstrated with CT and MRI studies (Fig. 2). We waited until partial neurological and cognitive recovery occurred, so that the patient could understand his situation. He was assisted by his wife and our rehabilitation team and especially by the neuropsychologist. However, there was no improvement of the ongoing complete arrest of spontaneous breathing and also very little change regarding his severe tetraparesis. Second craniovertebral operation was carried out on January 29, 2002. A dorsal approach was performed again; the bone grafts and the fixateur interne were removed because of loosening of the screws. A decompression by suboccipital craniectomy combined with an enlargement of the foramen magnum was completed with decompression by laminectomy C1; re-stabilization with the aid of plates and rods of the Vertex titanium system® from the occiput down to C2-C4 at the right and C2-C3 at the left side, combined with wire loops to secure the bone fusion was finally performed (Fig. 3**a**,**b**). During a subsequent functional neurorehabilitation the patient remained in halo- immobilization from February 11 until May 8. Then we had to take the halo away because of the patient's psychotic and claustrophobic reaction and an urgent wish of his family. With a cervical collar bracing for another 4 months X-ray investigation of the fusion segments demonstrated postoperatively stable conditions.

Continuous ventilation was necessary until January 30, thereafter intermittent ventilation and CPAP was needed for one month. He remained in the ICU until he was weaned off from the home ventilator which was achieved at the beginning of March. The postoperative course during intensive care treatment and early rehabilitation were uneventful, as it was thereafter during the following months of a functional neurorehabilitation in our specially designed department [4,8,10,11,13,18]. Here the

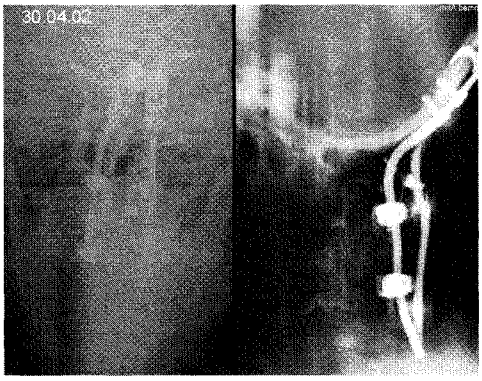


FIG. 3. Sagittal spiral CT three weeks after the first operation (21.01.02) demonstrates loosening of the implanted occipital screws and displacement of fixateur interne (Cervifix R) implants (black arrow) while the patient is under Crutchfield's tongue extension because of recurrent instability C0/C1). White arrow: Bone defect following transoropharyngeal decompression and resection of apex dens axis. 30.04.02, three months after second look operation the plain X-ray ap view and sagittal tomogram show the correct positioning of the hooks and plates of the Vertex system for craniocervial fusion from the occipital bone to C2-C4 right, and C2–3 left side while the patient is still immobilized by in Halo Fixateur

same interdisciplinary team took care of him until he was able to wash himself, to eat, to walk with help, until he was fully mobilised in his wheel chair, and had no cognitive or behavioural deficits and so fulfilled the cut off criteria of Phase B (early rehabilitation) regarding his functional assessment with the aid of the Early Rehabilitation Barthel Index (ERBI) >+40 points [11] and Functional independent Measure (FIM) >30 points [10]. After five months of early rehabilitation he was referred for further postacute and long term neurorehabilitation to another institute. The distally pronounced tetraparesis and marked muscle atrophy of the four limbs combined with a spinal ataxia improved over time, but the breathing was stable and completely normal again. After two years the patient was seen again and at that time he was completely reintegrated into social life and back to the military service in his country.

2 Discussion

Craniovertebral junction abnormalities can be developmental, genetic, or acquired in origin. They can cause a number of different symptoms and signs, including myelopathy, brain stem, cranial nerve, and cervical nerve root dysfunction; vascular insufficiency or any combination of these [1]. Locked-in syndrome is a rare postoperative complication when it can be due to compression of vascular system of the upper and lower brain stem [2–4]. The primary cause for this may be a congenital malformation of the craniovertebral junction which, after trauma, leads to a functional neurological impairment and severe instability. Functional neurorehabilitation is usually not mentioned in the orthopaedic and neurosurgical literature to overcome and to improve disturbed central nervous functioning (see the Algorithm for treatment of

craniovertebral abnormalities published by Van Gilder et al fig. 141–4 and table 147–2, pp 38–39 [1] despite the author's remark" The patient must remain in halo immobilization for 6–12 months after the procedure".

Rehabilitation [6,9,10,12,13] can reduce secondary complications while furthering spontaneous functional recovery and restoration of impaired sensory motor and mental-cognitive functioning that seems to be mainly based on brain plasticity [14]. Culyer et al [7], in 1971, have suggested three steps for gauging outcome from any kind of illness: (1) specific indicators, (2) devise measures and (3) agree values. Overall outcome has been demonstrated to be more dependent on mental-cognitive disabilities than on physical handicaps. There are four main indicators of final outcome: (1) removal of threat to life (immediate and future), (2) relief of symptoms (mental-cognitive and/or physical), (3) reduction of dependence (institution/home) and (4) social reintegration (work, leisure, mobility, joy) [7].

New developments in neurorehabilitation, for example a special neurosurgical unit for early rehabilitation as part of the general neurosurgical service as it has been introduced by the author for the first time ever in 1994 [8,10,13], can significantly improve the patients final outcome and further quality of life [7,12,15,16]. In the seventies the neurosurgeons became responsible for intensive care treatment of patients after craniocerebral trauma and difficult surgical procedures. The became aware about risks, complications and pathophysiology and achieved a much better early outcome. The same is true when they become responsible for functional rehabilitation of their patients during the acute and subacute stage of recovery and for neurosurgical re-engineering of brain and spinal cord lesions [14,17]. Neurosurgical rehabilitation is not a new but a widely forgotten tool. It has an old tradition in Europe and especially in Germany [15,18]. Our concept is based on early ideas of rehabilitation of sensory motor impairments, as it was formulated by Karl Otfrid Foerster (1873–1941) [15]. It respects therapeutic exercises of peripheral paresis and the physiotherapy of central motor disorders, differentiating between spastic and paretic components. In our patient the impairment was caused by post traumatic and surgical craniovertebral instability and vascular compression. Neuropsychological rehabilitation became an indispensable and major part of functional neurorehabilitation in neurosurgery to help improving the patient's cognitive status, emotional and motivational disturbances as well as psychosocial adjustments following the acute impact lesion of the brain and spinal cord [19–21] Prigatano quotes [22]: "The first principle of neuropsychological rehabilitation is that the clinician must enter the patient's phenomenological field in order to sense what he or she experiences.- Therapy aimed at the reducing of patient's frustration and confusion will be eagerly met by the patient (and the relatives), irrespective of whether such rehabilitation activities actually improve higher cerebral functions" (end of citation pp 28–29, 1999). Postoperative early rehabilitation in neurosurgery opens up a new venue for restoration of impaired neurological disorders as well as for neuropsychological, cognitive and behavioural functions [12,15].

Holistic rehabilitation, as we see it to day, covers the whole spectrum of neurological-neurosurgical rehabilitation (Fig. 4) [10]. Rehabilitation has to start straight after impact with the careful assessment of the functional impairment and the underlying pathophysiology by using all modern diagnostic tools. If necessary, it is combined with adequate operative procedure(s) and/or intensive care treatment.

FIG. 4. Holistic early neurosurgical neurorehabilitation to support functional recovery with daily physio- occupational- (ADL training) and neuroychological therapy at the ICU four weeks postoperatively: Two occupational therapists are needed for the first steps with the walker in at the floor of the ICU while the patient is still on an ambulatory battery driven respirator. Noteworthy is the spouse as part of the neurorehabilitation team (in the background). She guaranteed the best personal, social and cultural environment for her mentally and cognitive impaired, emotionally stressed husband during early rehabilitation, when he slowly emerged from coma and locked-in syndrome

This was successfully demonstrated in our case report with complete functional reintegration into social life. The principles have been classified with aid of the WHO ICF and require that rehabilitative interventions start in a multidisciplinary way which is corresponding to our standards for quality management in early neurological-neurosurgical rehabilitation [13]. Functioning, as defined by the WHO-ICF serves as an umbrella term encompassing all body functions, activities, and participations in social life (= quality of life). ICF defines components of health and some health-related components of well-being. These domains are described as from the perspective of the body, the individual, and the society in two basic lists: (1) *Body* functions and structures and (2) *Activities* and participation in the social life meaning to be mobile and to enjoy social contacts, emotions and play [11–14,21,23].

3 Conclusion

From the beginning of neurological surgery the preservation and restoration of impaired CNS and PNS functions have been the primary task for the physicians. This important fact demands that neurosurgeons must get involved with the issues of functional neurorehabilitation. I close this context and trust for continuing co-operation with the intensive care physicians, anaesthesiologist, neuro-radiologists and the early neurorehabilitation team as well as with the neurosurgeons from other hospitals of the area as they can all guarantee an indispensable help from the very onset of medical treatment for the brain, spine and spinal cord injuries and thus to achieve the patient's best functional outcome.

References

1. VanGilder JC, Menezes AH (2000) Craniovertebral abnormalities and their neurosurgical management. In: Schmidek HH, Sweet WH (eds) Operative neurosurgical techniques, indications, methods, and results, 4th edn, vol. 2. WB Saunders, Philadelphia, PA, pp 1934–1945

2. American Congress of Rehabilitation Medicine (1995) Recommendations for use of uniform nomenclature pertinent to patients with severe alterations in consciousness. Arch Phys Med Rehabil 76:205–209
3. Hartmann A, Wappenschmidt J (1986) Topographic analysis of neurology symptoms in brain stem diseases In: Samii M (ed.) Surgery in and around the brain stem and the third ventricle. Springer, Berlin, pp 105–128
4. Plum F, Posner JB (1980) The diagnosis of stupor and coma. FA Davis, Philadelphia, PA
5. Steriade M, McCarley RW (eds) (1990) Brainstem control of wakefulness and sleep. Plum Press, New York
6. Card WL (1975) Development of a formal structure for clinical management decisions; a methematical analysis. In: The Ciba Foundation (ed.) Outcome of severe damage to the central nervous system. Elsevier, Excerpta Medica, Amsterdam, pp 291–301
7. Culyer AJ, Lavers RJ, Williams A (1971) Social indicators: Health. Soc Trends 2:31–42
8. von Wild KRH (ed.) (1993) Spektrum der neurorehabilitation. W Zuckschwert Verlag, München
9. von Wild KRH (2000) Perioperative management of severe head injuries in adults (chapter 4). In: Schmidek HH, Sweet WH (eds) Operative neurosurgical techniques: Indications, methods, and results, 4th edn. Saunders Company, Philadelphia, PA, pp 45–60
10. Ortega-Suhrkamp E, von Wild KRH (2002): Standards of neurological-neurosurgical rehabilitation. Acta Neurochir (Vienna) [Suppl] 79:11–19
11. Schönle PW (1996) Frühe phasen der neurologischen rehabilitation. Differentielle schweregradbeurteilung bei patienten in der Phase B (frührehabilitation) und in der Phase C (frühmobilisation/postrimäre Rehabilitation) mit hilfe des frührehabarthel-index (FRBI). Neurol Rehabil 1:21–25
12. Ben-Yishay Y, Daniels-Zide E (2000) Examined lives: Outcome after holistic rehabilitation. Rehabil Psychol 45:112–129
13. von Wild KRH (2002): Neuro-rehabilitation—A challenge for neurosurgeons in the 21st century. Concepts and visions of the WFNS committee on neurosurgical rehabilitation. In: von Wild KRH (ed.) Functional Rehabilitation in neurosurgery and neurotraumatology. Acta Neurochir Suppl 79:3–10
14. Stein DG (2000) Brain injury and theories of recovery. In: Christensen AL, Uzzell BP (eds) International handbook of neuropsychological rehabilitation. Kluver Academic Plenum Publishers, New York, USA pp 9–32
15. Förster O (1936) Übungstherapie. In: Bumke O, Foerster O (Hrsg) (eds) Handbuch der neurologie, Bd 8. Springer, Berlin, pp 316–414
16. 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
17. von Wild KRH (ed.) (2005) Re-engineering of the damaged brain and spinal cord. Evidence-based neurorehabilitation. Acta Neurochir (Vienna) [Suppl] 93
18. von Wild KRH (2001) Neurochirurgie und neurorehabilitation—ein Beitrag zur geschichte der neurochirurgischen Rehabilitation. In: Deutsche Gesellschaft für Neurochirurgie (ed.) Neurochirurgie in Deutschland: Geschichte und Gegenwart 50 Jahre Deutsche Gesellschaft für Neurochirurgie. Blackwell Wissenschafts-Verlag, Berlin, pp 424, 428
19. Christensen AL, Uzzell BP (eds) (1988) Neuropsychological rehabilitation. Proceedings of the Conference on Rehabilitation of Brain Damaged People: Current knowledge and future directions, Copenhagen, June 15–16, 1987. Kluwer Academic Publishers, Boston, MA

20. Christensen AL, Uzzell BP (eds) (2000) International handbook of neuropsychological rehabilitation. Kluwer Academic/Plenum Publishers, New York, Boston, Dorfdrecht, London, Moscow
21. Goldstein K (ed.) (1919) Die behandlung, fürsorge und begutachtung der hirnverletzten. FCW Vogel, Leipzig
22. Prigatano GP (ed.) (1999) Principles of neuropysychological rehabilitation. Oxford University Press, New York, pp 28–29
23. 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

Functional Electrical Stimulation for Spinal Cord Injury Rehabilitation at the University of Virginia and Duke University

EDWIN COOPER[1], JAMES MCELHANEY[2], DI HAN[3], BRANAN COOPER[4], and BRYAN COOPER[5]

Summary. Functional electrical stimulation (FES) has applications in spinal cord injury to help restore function to patients with quadriplegic hands or paraplegic legs. Early experiences at the University of Virginia and Duke University are presented. Further progress has been obtained at multiple centers with computerized stimulation, miniaturization of components, and mind/machine interfacing. Knowledge gained from the early projects led to the concept of electrical stimulation of the median nerve to hasten awakening from coma.

Key words. electrical stimulation, spinal cord injury

FES has been used for over three decades to assist paraplegic patients in walking and for restoring grasp to quadriplegic persons. In 1973 Cooper, Bunch and Campa at the University of Virginia reported on attempts to restore paraplegic ambulation using radio-linked implanted electrodes on the femoral and sciatic nerves of a paraplegic young man. Four radio-linked electrodes were implanted sequentially on the femoral and sciatic nerves of a 19-year-old paraplegic male five to seven months after fx-dislocation of T11-12 with complete spinal cord injury from a fall on May 19, 1972. Chronic electrical nerve stimulation (Neurostimulator, Avery Laboratories, Inc.) was performed with a radio frequency signal of 2.1 MHz which was converted by implanted receivers into a biphasic pulse of 0.2 milliseconds duration and 2 volts delivered through bipolar platinum electrodes.

Initial muscle function of the quadriceps was "trace plus." Electromyographic studies at time of first implantation showed denervation potentials in all muscles with no voluntary or reflex-induced muscle potentials.

[1] Department of Neurological Surgery, University of Virginia, Charlottesville, VA, 1001 North Queen Street, Kingston, NC 28501, U.S.A., [2] Retired Chairman of Department of Biomedical Engineering, Duke University, Durham, NC, U.S.A., [3] Industrial Engineer, Raleigh, NC, U.S.A., [4] VOQUEST Project in Biomedical Engineering, Duke University, Durham, NC, and [5] East Carolina Neurology, Brody School of Medicine, East Carolina University, Greenville, NC, U.S.A.

Histochemical studies of right quadriceps biopsy specimens demonstrated severe and uniform denervation atrophy involving all but about 20 fibers in the entire specimen. There was no selectivity of fiber type. Targetoid formations were present in many of the type I fibers. The left quadriceps biopsy specimen was similar. Thus, the electromyogram and histochemical studies demonstrated severe but incomplete lower motor neuron involvement.

The quadriceps were stimulated for 10 h/day. After two months the strength had increased from "trace plus" to "fair." Four months after implantation EMG (electromyogram) still showed denervation in virtually all muscle sites. Other polyphasic high-amplitude, long-duration potentials suggesting reinnervation were also seen.

Muscle biopsy after ten weeks of stimulation showed an increased proportion of muscle fibers (25%) with normal or hypertrophic size with residual denervation involving about one half of the fibers. There were no changes in the histochemical characteristics [1].

By means of alternating sciatic nerve stimulation (triggered either by a hand-controlled toggle switch or a positionally activated mercury switch), ambulation for about 40 feet in a modified walker with a seat was accomplished. These first few steps across the room over thirty years ago may have been the first recorded for a paraplegic individual attempting to ambulate under electrical control. It was concluded over 30 years ago that chronic electrical neuromuscular stimulation was beneficial for paraplegic persons.

In the decades after the lower extremity electrode implantation at UVa, more refined techniques for paraplegic ambulation were employed at multiple centers. Especially noteworthy were the developments by Marsolais at Case Western Reserve and Petrofsky at Wright State University [2,3].

In the late 1980s, at the Duke Department of Biomedical Engineering, individuals with quadriplegia used voice-activated computerized electrical stimulation to control paralyzed forearm and hand muscles. Pioneering upper extremity FES research has been done by Clippinger in the 1970's at Duke Hospital. He implanted radio-linked electrodes on the median nerve in the forearms of patients with traumatic hand amputations. This provided sensory feedback from a prosthetic hand device.

In the 1987–88 VOQUEST pilot project (Voice Operated QUadriplegic Electrical STimulation) at Duke University, Department of Biomedical Engineering, high speed computerized discrimination of vocalized patterns provided an effective control-mechanism for multiple electrode sites to produce semi-voluntary hand function in quadriplegic users [4].

Four adult quadriplegic subjects ranging from six months to six years post cervical fracture dislocation participated in the VOQUEST project. Two pairs of two inch square lubricated rubber electrodes were applied to the volar and dorsal surfaces of the right forearms of the subjects. Programmed electrical stimulation was done in their homes eight hours daily for three months using a Respond II Medtronic neuromuscular stimulator. Serial electronic measurements of muscle contraction force were made above and below the level of the paralysis biweekly. Subjects were examined and interviewed regularly by a team of biomedical engineers, physical and occupational therapists and physicians.

In the second three month phase, pairs of electrode sites were mapped on the conditioned forearms to produce desired hand movements. Three pairs of volar

electrodes triggered thumb, combined finger and wrist flexion. A dorsal pair caused simultaneous wrist and digital extension. Firm one inch square convex electrodes were built into a plastic forearm orthosis custom made for each subject.

The voice control system consists of an IBM-PC/AT computer and Texas Instrument (TI) speech unit installed in the computer with a custom stimulator/switching interface circuit. The TI speech board recognized verbal commands, and a control program then selected the appropriate locations and levels of stimulation via the switching interface.

Increases in the force of contraction in response to electrical stimulation of the chronically stimulated forearm and hand muscles were noted. There was no increase in strength of the contralateral hand. Also increases in the strength of the ipsilateral proximal arm muscles that were innervated above the level of the cervical spinal cord injury were found in two subjects. But a surprising finding was a slightly greater rise in the contractile force of the unstimulated contralateral arm. This increase was noted in the muscles under voluntary control above the neural lesion, but not in the paralyzed muscles of the contralateral distal arm. The hand motions elicited by computerizing electrical stimulation under voice control were slow and awkward in the VOQUEST project [4].

Routing the pulsed electrical stimulation to electrodes (surface or implanted) in paralyzed arms and legs has included simple off/on switches, shoulder switches, and myoelectrical control [1,5,6]. The voice recognition computerized switching system that was developed at Duke University in 1988 was a step closer to conscious control of a paralyzed limb [7]. Future applications could be modeled after brain/machine interfaces (BMI).

In this 21st century at the Pratt School of Engineering at Duke, monkeys consciously control the movements of a robot arm using signals from their own brains picked up by implanted electrodes [8,9]. Groups of microwires in multiple arrays were surgically implanted in two adult female monkeys in several frontal and parietal cortical areas including the dorsal premotor cortex, the supplementary motor area, and the primary motor cortex in both hemispheres. With training and the plasticity of the monkey brains with continuous visual feedback of the gripping force, the monkeys were able to operate a robot arm [8].

The principal investigators at Duke were Nicolelis (neurobiology professor) and Henriquez (biomedical engineer). There is ongoing work, a project to develop human brain interfaces. These applications could aid quadriplegic and paraplegic subjects to regain control of paralyzed muscles with a combination of the brain implants and the implanted electrical stimulation systems [9].

The evolution of the electrical stimulation at UVa in the 1970's with efferent stimulation to strengthen paraplegic legs and at Duke (1980's) for efferent/afferent stimulation to strengthen and control quadriplegic hands by voice commands, led to the concept of afferent stimulation to "re-boot" the injured comatose brain. The observation in the VOQUEST project about left to right hemispheric transfer via the corpus callosum led to the development of median nerve electrical stimulation for coma arousal [10]. This crossover effect discovered in the Duke BME Lab led to the concept of peripheral nerve stimulation to influence comatose brain reawakening.

Over the past dozen years, beginning with pilot projects at the medical center of East Carolina University and the Department of Neurosurgery at the University of

Virginia, right median nerve stimulation has been used to hasten awakening from deep coma after severe closed head injury [10,11]. The concept of median nerve stimulation has been readily accepted in Asia. The important neurophysiological and clinical research in clinical work on coma arousal by spinal cord electrical stimulation has been done by Professor Kanno (Fujita Health University, Toyoake, Japan) and colleagues [12,13].

1 Conclusion

For the past three decades, electrical stimulation of viable neural tissue has been used to bypass the damage produced by trauma in the spinal cord. Peripheral nerve stimulation also can be effective in cases of partial spinal cord injury, whether chronic or acute. Biomedical engineering applications of micro-electrodes in the brain will allow for control of peripheral nerves, regaining control of paralyzed limbs in quadriplegic and paraplegic persons. Recent projects have involved electrical stimulation of the peripheral nerves to influence the recovery of the injured central nervous system for coma awakening. Neural plasticity remains a viable reality in adult quadriparetic and comatose patients.

References

1. Cooper E, Bunch W, Campa J (1973) Effects of chronic human neuromuscular stimulation. Surg Forum 24:477–479
2. Marsolais E, Kobetic R (1987) Functional electrical stimulation for walking in paraplegia. J Bone Joint Surg 69-A:728–733
3. Petrofsky J, Philips C, Larson P, et al (1985) Computer synthesized walking: An application of orthosis and functional electrical stimulation (FES). J Neurol Orthop Med Surg 6:219–230
4. Cooper E, Han D, McElhaney J, et al (1988) A voice controlled computer system for restoring limited hand functions in quadriplegics. Proceedings AVIOS voice input/output systems applications conference. San Francisco, CA
5. Peckham P, Mortimer J, Marsolais E (1975) Controlled prehension and release in the C5 quadriplegic humans following exercise induced by chronic electrical stimulation. Clin Orthop 114:326–334
6. Peckham P, Keith M, Kilgore K (1999) Functional electrical stimulation. Spinal Cord Inj Rehabil 5:33–34
7. Gersh M (1992) Electrotherapy in rehabilitation. Davis Company, Philadelphia, PA, p 260
8. Carmena J, Lebedev M, Crist R, et al. (2003) Learning to control a brain-machine interface for reaching and grasping by primates. PLoS Biol 1:e42
9. Henriquez C (2004) Brain-machine interface. Duke BME News 3:1–2
10. Cooper J, Jane J, Alves W, et al. (1999) Right median nerve electrical stimulation to hasten awakening from coma. Brain Inj 13:261–267
11. Cooper E, Cooper J (2003) Electrical treatment of coma via the median nerve. Acta Neurosurgica 87:7–10
12. Kanno T, Kamei Y, Yokoyama T (1992) Treating the vegetative state with dorsal column stimulation. Soc Treat Coma 1:67–75
13. Yokoyama T, Kamei T, Kanno T (1996) Right median nerve stimulation for comatose patients. Soc Treat Coma 5:117–125

Treatment Results of Poor-grade (WFNS Grade V) Patients with Subarachnoid Hemorrhage

Takehiko Sasaki, Joji Nakagawara, Toshiaki Osato, Kazuyuki Hayase, Rihei Takeda, and Hirohiko Nakamura

Summary. We reviewed our treatment results of poor-grade (WFNS grade V) patients with subarachnoid hemorrhage and analyzed factors related to outcome. Forty-six consecutive patients of WFNS grade V with subarachnoid hemorrhage from ruptured cerebral aneurysm are reviewed retrospectively. We applied surgical or intravascular intervention for patients with GCS better than 4 and pupillary reaction or with GCS 3 on admission improved better than 4 after initial medical treatment. Three-month outcome was evaluated by GOS and factors affected to the outcome were analyzed. Only 2 of 21 patients treated conservatively were survived. Two patients treated with CSF drainage were died from rerupture. Direct surgical intervention for aneurysms were applied in 23 patients by surgical clipping in 20 and GDC coil embolization in 3. Favorable outcome better than MD was obtained in 9 of 23 (39%) patients. Neurological improvement during early stage of initial medical treatment, presence of localized intracerebral hematoma and acute hydrocephalus were predictive of better outcome, while association of massive intracerebral hematoma or intraventricular hematoma were signs of poor outcome.

Key words. subarachnoid hemorrhage, WFNS grade, early surgery, intracerebral hematoma, intraventricular hematoma

Although surgical treatment of poor-grade patients with ruptured cerebral aneurysms is still challenging, it is well known that some patients become independent after surgical intervention. Controversy is how to select patients with factors predictive of favorable outcome. The purpose of this paper is to extract factors predictive of favorable or poor outcome from analysis of our treatment results.

Department of Neurosurgery, Nakamura Memorial Hospital, 1 Minami, 14 Nishi, Chuo-ku, Sapporo 060-8570, Japan

1 Clinical Material and Methods

Consecutive 46 patients with subarachnoid hemorrhage whose Glasgow Coma Scale were 6 or less are the material of this study. All were transferred to Nakamura Memorial Hospital between January 2000 to September 2002 and had evidence of subarachnoid hemorrhage by CT. Patients with obvious bleeding source other than cerebral aneurysm were excluded. Twelve were male and 34 were female, and mean age was 64.8 years.

Our indication criteria of direct surgery is GCS 4 or better or GCS 3 followed by clinical improvement during initial medical treatment. Initial medical treatment consists of respiratory and circulation support, blood pressure control and reduction of intracranial pressure by administration of mannitol or glycerol.

We analyzed the contribution of each factor, such as change of neurological status during initial medical treatment, pupillary response, acute hydrocephalus, intracerebral hematoma and packed intraventricular hematoma, to outcome of three month.

2 Results

2.1 Overall Results

Twenty-three of 46 patients underwent conservative or tentative treatment. Reasons why they did not undergo direct surgical intervention are described in Table 1. Twenty-one patients were treated conservatively. Among them, 19 were dead and the others were worse than SD. Two patients underwent tentative CSF drainage and both were dead by rerupture after CSF drainage without any chance of direct surgery. The outcomes of all patients treated with conservative or tentative fashion were worse than severe disability (SD) and their mortality rate was 91.3% (Table 1). On the other hand, direct surgical intervention was attempted in 23 of 46. Twenty patients underwent direct surgical clipping and 3 underwent endosaccular coil embolization. Outcome of them was good recovery (GR) in 4, moderate disability (MD) in 5 and mortality rate was 17.4%. Nine of 23 (39.1%) patients who were able to be applied direct surgical intervention became independent (Table 2).

TABLE 1. Outcome of patients with conservative or tentative treatment

		GR	MD	SD	V	D
Conservative						
GCS 3 without improvement	13					
Decline to GCS 3 by rerupture	5					
Over 80 years	2					
Vertebral artery dissection	1					
	21	0	0	1	1	19
Tentative (CSF drainage)						
GCS 3 without improvement	2					
		0	0	0	0	2
Total	23	0	0	1	1	21
						91.3%

TABLE 2. Outcome of patients with direct surgical intervention

		GR	MD	SD	V	D
Clipping	20					
Coil embolization	3					
Total	23	4	5	8	2	4
			39.1%			17.4%

TABLE 3. Neurological change and outcome in patients with direct surgical intervention

		GR	MD	SD	V	D
Improved after initial treatment	7	2	1	4	0	0
Stable	12	2	3	3	1	3
Decline	4	0	1	1	1	1
Total	23	4	5	8	2	4

TABLE 4. Pupillary response, acute hydrocephalus, intracerebral hematoma (ICH) and intraventricular hematoma (IVH) and outcome

		GR	MD	SD	V	D
Pupillary response: preserved	13	4	5	2	1	1
Pupillary response: absent	10	0	0	6	1	3
Acute hydrocephalus	5	1	2	1	0	1
Localized ICH	6	1	3	2	0	0
Massive ICH	5	0	1	2	1	1
Packed IVH	3	0	0	2	0	1

2.2 Neurological Change and Outcome

While 3 of 7 patients with neurological improvement during initial medical treatment became better than MD, only one of 4 patients with neurological decline during initial medical treatment became better than MD. Although 2 of 4 patients who obtained good recovery showed some neurological improvement during initial medical treatment, all vegetative of dead patients never experienced neurological improvement (Table 3).

2.3 Pupillary Response, Acute Hydrocephalus, Intracerebral and Intraventricular Hematoma

In 13 patients with preserved pupillary response, 9 were better than MD, and all patients with favorable outcome had preserved pupillary response. Three of 5 (60.0%) patients with acute hydrocephalus and 4 of 6 (66.7%) patients with localized intracerebral hematoma became independent, on the other hands, 4 of 5 (80.0%) patients with massive intracerebral hematoma and all 3 patients with packed intraventricular hematoma were worse than SD (Table 4).

3 Discussion

Although benefits of early surgical intervention for subarachnoid hemorrhage from ruptured cerebral aneurysms are established in patients with good or moderate neurological grade [1], it is still challenging for patients with poor neurological grade. Some authors report favorable outcome could be obtained in some patients with poor neurological grade [2], but indication of direct surgical intervention in early stage is controversial. Our indication for WFNS grade V patients is consisted with consciousness level and pupillary response which represent global cerebral and brain stem function. Except for 2 patients older than 80 and 1 patients with dissecting vertebral aneurysm, 23 of all patients were with initial WFNS grade V were treated by conservative or tentative fashion because of deep coma without any improvement during initial medical treatment or neurological decline by early rerupture. Their outcome was miserable and mortality rate was 91.3%. The other half underwent direct surgical intervention to ruptured aneurysms because of their neurological status better than GCS 4 or improved during initial medical treatment from GCS 3. Favorable outcome obtained in 39.1% of those and mortality rate was 17.1%.

As described in previous reports, neurological improvement during early stage brings possibility of direct surgery and prediction of outcome in poor grade patients [3,4]. From our results, favorable outcome obtained in 42.9% of patients with neurological improvement during initial medical treatment before direct surgical intervention. Direct surgical intervention gives possibilities to become independent for patients with neurological improvement during initial medical treatment even when their primary neurological grade are poor.

Preservation of pupillary response was proved to be essential for favorable outcome. Preservation of pupillary response indicates that midbrain is functioning, and preservation of midbrain function might be essential for recovery to be independent.

Presence of acute hydrocephalus and localized intracerebral hematoma was the signs of favorable outcome. As the brain dysfunction from acute hydrocephalus and localized intracerebral hematoma might be reversible, early surgical intervention has possibilities to bring functional recovery.

On the other hands, massive intracerebral hematoma and packed intraventricular hematoma were the signs of poor outcome. Effect of early surgical removal of intraventricular hematoma is limited, and massive clots in aqueduct and fourth ventricle may bring irreversible damage to surrounding brain stem.

4 Conclusions

Early surgical intervention is treatment of choice even for patients with poor neurological grade. Neurological improvement during initial medical treatment is a sign to recommend early surgical intervention. Preservation of pupillary response is essential for favorable outcome. While presence of acute hydrocephalus and localize intracerebral hematoma indicates better outcome, massive intracerebral hematoma and packed intraventricular hematoma suggest limitation of functional recovery.

References

1. Haley EC, Kassell NF, Torner JC, et al (1992) The international cooperative study on the timing of aneurysm surgery. The north American experience. Stroke 23:205–214
2. Kobayashi N, Kamiyama H, Tanikawa R, et al (1996) Treatment and results in poor-grade aneurysm patients. Surg Cereb Stroke 24:101–106
3. Suzuki M, Otawara Y, Doi, M, et al (2000) Neurological grades of patients with poor-grade subarachnoid hemorrhage improve after short-term pretreatment. Neurosurgery 47:1098–1105
4. Sato M, Kodama N, Sasaki T, et al (2000) Analysis of patients with grade up of Hunt and Kosnik grade IV, V in the acute stage. Surg Cereb Stroke 28:371–374

Minimally Invasive Spinal Surgery Using Instrumentation

Hiroyuki Nakase, Yuki Ida, Young-Su Park, Hidehiro Hirabayashi, Shoichiro Kawaguchi, and Toshisuke Sakaki

Summary

Background and Purpose: With the advance of better optics and operative equipment, image-guided systems, new biological agents, and instrumentation systems, spinal surgery can now be performed in a minimally invasive way. We report our concept and recent cases of less invasive spinal surgery using instrumentation.

Method and Results: We used spinal instrumentation in 174 cases among recent 581 cases for cranio-cervical junction cervical, thoracic and lumbar lesions. The instrument were used for occipito-cervical and anlanto-axial fixation (21 cases), anterior and posterior reconstruction for cervical disorders (127 cases), and thoracic and lumbar fixation (26 cases). Satisfactory improvement as scored on the Neurosurgical Cervical Spine Scale (NCSS) and Japanese Orthopedic Association (JOA) scale, and complications in spinal instrumentation cases were examined compared with non-instrumentation cases. There are no differences in the surgical result and complication rate, but average hospitalization time is significantly shorter in cases with instrumentation (121 cases) than without instrumentation (115 cases) in cases of anterior reconstruction of the cervical spine ($P < 0.01$).

Conclusions: Minimally invasive surgical procedure using spinal instrument with appropriate patient selection may raise the cost of the operation, but can be undertaken with acceptable mortality and morbidity rate and offer short hospital stay and quicker return to work by immediate stabilization.

Key words. minimally invasive surgery, spinal surgery, instrumentation

Department of Neurosurgery, Nara Medical University, 840 Shijo-cho, Kashihara, Nara 634-8522, Japan

1 Introduction

In the past decade, there has been a substantial increase in interest in minimally invasive procedures in all areas of medicine, particularly for spinal disorders. The terms "*minimally invasive surgery*" have been used to describe surgical approaches or operations that are performed with less trauma to anatomical structures on the way to the surgical target area. Minimally invasive surgery is not simply reduction in the size of the skin incision, but rather reducing to a minimum the physical trauma inflicted on the patients [1–4].

Thanks to the advance of better optics and operative equipment, image-guided systems, and new biological agents, a minimally invasive spinal surgery can now be performed. In particular, the modern development of spinal instruments is also useful for minimal invasive way. Recent minimally invasive spinal surgery include cervical cage, key hole approach, endoscopy, unilateral laminoplasty, and skip laminoplasty in cervical lesions and vertebroplasty, Micro-endoscopic-discectomy (MED), unilateral approach, minimally invasive anterior lumbar interbody fusion (Mini-ALIF) in thoracolumabr lesions, etc [5–8].

We report our concept and recent spinal lesions operated in less invasive way using instrumentation.

2 Material and Methods

We used spinal instrumentation in 174 cases among recent 581 cases for craniocervical junction cervical, thoracic and lumbar lesions. The instrument were used for occipito-cervical and anlanto-axial fixation (21 cases), anterior and posterior reconstruction for cervical disorders (127 cases), and thoracic and lumbar fixation (26 cases). Satisfactory improvement as scored on the Neurosurgical Cervical Spine Scale (NCSS) and Japanese Orthopedic Association (JOA) scale, and complications in spinal instrumentation cases were examined compared with non-instrumentation cases.

In cases of anterior reconstruction of the cervical spine, we compare between cases with instrumentation (group A; 121 cases, 178 discs) and cases without instrumentation (group B; 115 cases, 163 discs).

3 Results

Recent minimally invasive spinal surgery in our institute include cervical cage and unilateral laminoplasty in cervical lesions (Fig. 1) and vertebroplasty, METREX (Fig. 2**a,b**), unilateral approach (Fig. 2**c**), Mini-ALIF (Fig. 3) for all patients requiring anterior lumbar interbody fusion in thoracolumabr lesions, etc. Also, we have performed "anterior cervical stabilization without harvesting of autologous bone grafts" to avoid the complication related to graft harvesting (Fig. 4) [9].

In cases of anterior reconstruction of the cervical spine, there are no differences in the surgical result (NCSS; 9.2 ± 1.4 in group A and 9.3 ± 1.4 in group B) (Fusion rate; 89% in group A and 94% in group B) and complication rate, but average hospitalization time is significantly shorter in cases with instrumentation than without

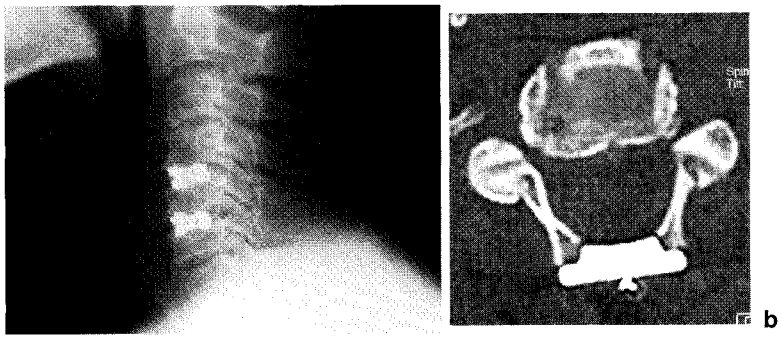


FIG. 1. **a** Lateral X-ray demonstrated anterior cervical fusion with threaded cages at C4-C5 and C5-C6. **b** Postoperative computed tomography (CT) shows bilateral open-door cervical expansive laminoplasty with hydroxyapatite spacers and titanium screw

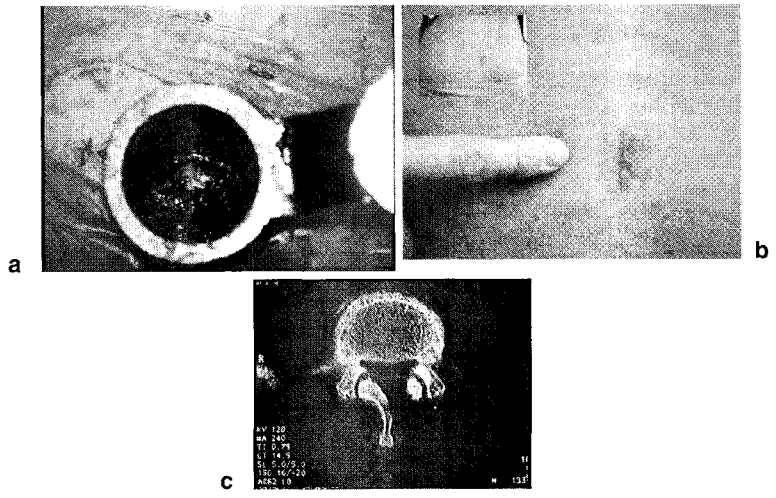


FIG. 2. **a** Intraoperative view of METREX. **b** Lumbar disc hernia can be performed via just one finger skin incision and split the muscle. **c** Postoperative computed tomography of unilateral approach for lumbar canal stenosis

instrumentation in cases of anterior reconstruction of the cervical spine (18 ± 6.4 days in group A and 27 ± 8.7 days in group B, $P < 0.01$) [10].

4 Discussion

Minimally invasive surgical procedures are usually performed with the help of recent progress in optical and imaging devices and to the development of instrumentations specifically designed for insertion via minimally invasive approaches

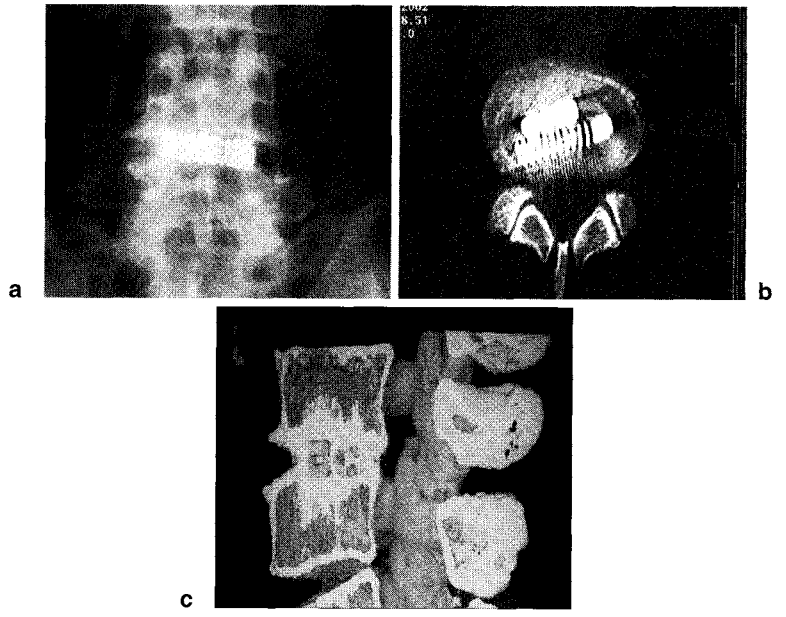


FIG. 3. X-ray (a) and CT (b) show minimally invasive anterior lumbar interbody fusion. Three dimensional (3D)-CT (c) demonstrated successful bone fusion around two types of cages three months after the operation

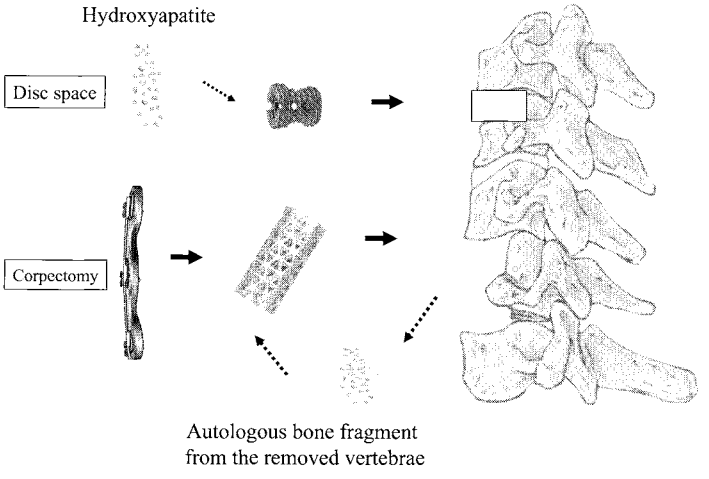


FIG. 4. Schema of anterior cervical stabilization using instrumentations without harvesting of autologous bone grafts. Threaded cage was filled with hydroxyapatite and mesh cage with autologous bone fragment taken from the removed vertebra

[1,2]. Within the last 10 years, such techniques have been developed in the field of spinal surgery. Minimal access spinal technologies aim primarily at minimizing the trauma associated with surgical exposure of the spine, decreasing postoperative morbidity, less blood loss, earlier rehabilitation, and acceptable complication rates.

Then, the patients benefit from the decreased postoperative pain, shorter hospital stay, and expedited return to normal activities. However, no published scientific studies have fully proved that minimally invasive techniques are superior over standard techniques. In my opinion, we should learn these minimally invasive techniques in a step-by-step fashion, starting with a conventional skin incision and, once the surgeon is familiar with the procedures and instruments, moving on to the invasive techniques to avoid any possible technique-related complications.

We also have recently performed minimally invasive spinal surgery as shown in this manuscript. Using METREX, removal of lumbar disc hernia can be performed via just one finger skin incision and split the muscle [5]. Percutaneous vertebral augmentation, including vertebroplasty and kyphoplasty, has become the treatment of choice for many patients with intractable back pain secondary to vertebral insufficiency fractures [6]. Spinal injections are important for evaluating and managing spinal pain and can be extremely useful diagnostically and therapeutically [2]. This article mainly describes less invasive techniques using instrumentation. We already reported the surgical results of anterior cervical stabilization using instrumentations without harvesting of autologous bone grafts compared with traditional technique, and concluded that the technique without grafts presented good clinical results and helped to avoid complications from the iliac crest donor site [9,11].

In conclusion, minimally invasive spinal surgery using instrument with appropriate patient selection may raise the cost of the operation, but can be undertaken with acceptable mortality and morbidity rate and offer short hospital stay and quicker return to work by immediate stabilization.

References

1. Assaker R (2004) Minimal access spinal technologies: State-of-the-art, indications, and techniques. Review. Joint Bone Spine 71:459–469
2. Deen HG, Fenton DS, Lamer TJ (2003) Minimally invasive procedures for disorders of the lumbar spine. Mayo Clin Proc 78:1249–1256
3. Jaffray B (2005) Minimally invasive surgery. Review. Arch Dis Child 90:537–542
4. Thongtrangan I, Le H, Park J, et al (2004) Minimally invasive spinal surgery: A historical perspective. Neurosurg Focus 15;16(1):E3:1–10
5. Cervellini P, De Luca GP, Mazzetto M, et al (2005) Micro-endoscopic-discectomy (MED) for far lateral disc herniation in the lumbar spine. Technical note. Acta Neurochir Suppl 92:99–101
6. Grohs JG, Matzner M, Trieb K, et al (2005) Minimal invasive stabilization of osteoporotic vertebral fractures: A prospective nonrandomized comparison of vertebroplasty and balloon kyphoplasty. J Spinal Disord Tech 18:238–242
7. Mayer HM (1997) A new microsurgical technique for minimally invasive anterior lumbar interbody fusion. Spine 22:691–699
8. Mayer HM (2000) The ALIF concept. Eur Spine J 9 (Suppl 1):S35–43

9. Nakase H, Park YS, Tei R, et al (2003) Anterior cervical stabilization without harvesting autograft. Jpn J Neurosurg (Tokyo) 12:670–675 (in Japanese)
10. Ida Y, Morimoto T, Nakase H, et al (2001) Instrumentation surgery for anterior reconstruction of the cervical spine. Spinal Surg 15:105–110 (in Japanese)
11. Nakase H, Ida Y, Tei R, et al (2002) Anterior cervical corpectomy and stabilization using titanium mesh cage and locking plate for muti-level disease of the cervical spine. Spinal Surg 16:105–111 (in Japanese)

Clinical Experience with Endoscope-controlled Removal of Intrameatal Vestibular Schwannomas

Tomokatsu Hori, Takashi Maruyama, and Mikhail Chernov

Summary. Use of endoscopes for surgery of the cerebellopontine angle tumors steadily obtains a widespread acceptance. We evaluated safety of the endoscope-controlled microneurosurgical removal of the intrameatal vestibular schwannomas through retrosigmoid approach, which was performed in 33 consecutive patients. Bayonet-style rigid endoscope with 70° angle of view and 4 mm of outer diameter was used for observation of the internal auditory canal. Its insertion in the cerebellopontine cistern was done under control through operating microscope. Endoscope-controlled manipulations necessitated use of the special holder system, which provided stable position of the device and allowed bimanual manipulations of the surgeon. In overall, 28 tumors underwent total removal, and anatomical preservation of the facial nerve was attained in 31 cases. Use of endoscope permitted removal of the neoplasm from the most lateral part of the internal auditory canal and precise identification of the nerve of tumor origin. In 8 out of 16 patients, who showed serviceable hearing before surgery, it was preserved after tumor removal. Therefore, endoscope-controlled removal of the intrameatal vestibular schwannomas seems to be technically feasible, effective and safe procedure. However, good equipment and special training are essential for attainment of optimal results.

Key words. neuroendoscopy, vestibular schwannoma, endoscope-controlled removal, internal acoustic meatus, outcome

1 Introduction

Since recently, there is growing interest in the use of neuroendoscopes during surgery for cerebellopontine angle (CPA) tumors [1–12]. Modern devices, both rigid and flexible, provide a wide angle of view, superb illumination with a cold light, and perfect

Department of Neurosurgery, Neurological Institute, Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan

depth of focus in conquer with high magnification. Its use during microsurgical procedures allow to reduce the size of the craniotomy, to improve visualization in the operative field, and to look around important anatomical structures eliminating the need for extensive retraction [2,9–11].

The advantages of the *endoscopic inspection* during or after microsurgical removal of vestibular schwannomas had been highlighted in several previous reports. These include early identification of the cranial nerves in the CPA, possibility of revision of the most lateral part of the internal auditory canal (IAC) for presence of the residual neoplasm, and visualization of the non-sealed petrous bone air cells for prevention of the postoperative cerebrospinal fluid (CSF) leak. With adjunct of endoscopy tumors can be removed more completely, with less morbidity, and degree of their resection can be assessed more precisely [1,5,8,11]. The length of drilling of the posterior wall of the IAC can be reduced, and inadvertent opening of the intraosseous endolymphatic sac and posterior semicircular canal, which has a crucial importance in hearing-preservation vestibular schwannoma surgery, can be avoided [7–10].

Meanwhile, the efficacy of *endoscope-controlled removal* of vestibular schwannomas is not clear yet. Moreover, there is some concern about possible endoscope-related complications due to poor overview of the operative field, limited two-dimensional image, and possible local increase of temperature in the vicinity to the tip of the device [8,9,11]. During 2004–2005 the senior author performed endoscope-controlled microneurosugical removal of 33 intrameatal vestibular schwannomas. The analysis of this clinical experience is presented herein.

2 Materials and Methods

Endoscope-controlled removal of vestibular shwannomas was performed in 23 women and 10 men, whose age varied from 22 to 77 years (mean: 50 ± 15 years). The tumor was located on the left side in 16 cases, and on the right side in 17. There were 31 initially diagnosed and 2 recurrent neoplasms. Three schwannomas were purely intrameatal, 8 had limited extension into the CPA, 7 filled the CPA completely, but did not show compression of the brain stem, and 15 caused more or less prominent brain stem compression. Before surgery 31 patients had either normal, or nearly normal facial nerve function, and 16 had serviceable hearing on the side of the tumor.

2.1 Surgical Technique

All surgeries were planned as routine microneurosurgical operations and if necessary could be completed without use of endoscope. General anesthesia, lateral oblique position of the patient, standard retrosigmoid approach, motor and somatosensory evoked potentials, auditory brain response, facial nerve monitoring, and cochlear nerve action potentials were used routinely, in the same way as described elsewhere [11,12].

After microsurgical intracapsular debulking of the tumor in the CPA, the posterior wall of the IAC was removed by high-speed drill. Bayonet-style rigid endoscope with 70° angle of view and 4 mm of outer diameter (Karl Storz GmbH & Co., Tuttlingen, Germany) fixed in the specially designed endoscope holder "EndoArm" (Olympus Co.,

Tokyo, Japan) was inserted into CPA under control through the operating microscope. Subsequent removal of the residual tumor from the CPA and IAC was attained utilizing concurrently both microscope- and endoscope-controlled technique with the use of routine microneurosurgical instruments. Regular irrigation of the wound by Ringer-lactate solution was done during use of the endoscope.

3 Results

Total tumor removal was attained in 28 cases, subtotal in 3, and partial in 2. Use of endoscope permitted removal of the residual tumor from the most lateral part of the IAC. Anatomical preservation of the facial nerve was attained in 31 cases. In 8 out of 16 patients, who showed serviceable hearing pre-operatively, it was preserved after tumor removal.

3.1 Complications

In one case the facial nerve was mechanically damaged by endoscope itself, which necessitated its direct suturing in the CPA. No one case of thermal injury to the cranial nerves, postoperative CSF leak, or infection was observed.

4 Discussion

4.1 Endoscope-controlled Removal of Vestibular Schwannomas

While endoscopic inspection during surgery for vestibular schwannomas obtained widespread acceptance, the advantages of endoscope-controlled removal of these tumors are less clear. Wackym et al [11] and Magnan et al [12] advocated use of this technique for dissection of the residual neoplasm from the most lateral part of the IAC. Goksu et al [8] reported the results of such procedures in 8 patients with serviceable hearing and small intrameatal vestibular schwannomas: total removal, functional preservation of the facial nerve, and anatomical preservation of the cochlear nerve was attained in all cases, whereas useful hearing was preserved in four. In the present series, which included a significant proportion of large tumors, total removal of the neoplasm was attained in 85% of cases, anatomical preservation of the facial nerve in 94% of cases, and preservation of the serviceable hearing in 50% of those, who showed its presence before surgery.

4.2 Lessons Learned

Several lessons had been learned from our clinical experience. First, use of rigid endoscopes, which are usually recommended for endoscope-assisted skull base surgery, may be complicated during endoscope-controlled procedures due to nearly coaxial positions of the endoscopic device and microinstruments. This disadvantage can be overcome if bayonet-style endoscopes and microinstruments are used. Second, several endoscopes should be available during surgery and used according to the particular goals. While 0°, 30°, and 70° angle of view endoscopes were found to be useful for

manipulations in the CPA, only the latter device was suitable for observation of the IAC. Third, angled rigid endoscopes may be difficult to pass in the operative wound without risk of inadvertent damage to the neurovascular structures [3,4]. Mechanical injury of the facial nerve by endoscope was met once in the present series. Therefore, we strongly recommend microscopic guidance during insertion of the 70° angle of view device into the CPA.

4.3 Risk of Thermal Injury: Is It Significant?

There is known concern, that prolonged use of endoscope can be accompanied by increase of the local temperature in the vicinity to its tip followed by thermal injury to the critical neurovascular structures [9,11]. However, the special thermographic study, which we conducted in the anatomical laboratory, revealed, that the local temperature in the CPA during the use of endoscope connected with a working light source, is much lower, comparing with those during removal of the posterior wall of the IAC by high-speed drill (unpublished data). In no one case of our clinical series thermal injury to the cranial nerves was marked. Definitely, the possibility of the complication may depend on the model of the device, duration of its use, type of the light source, and individual sensitivity of the cranial nerves. However, in general, the risk of thermal injury during use of endoscope should not be considered too high, and regular irrigation of the wound by Ringer-lactate solution seems to serve as a sufficient preventive measure.

4.4 Importance of the Endoscope Holder System

Intracranial neuroendoscopic procedures are usually performed through a narrow corridor in the vicinity to important neurovascular structures. While endoscopic inspection can be done by freehand fixation of the device, endoscope-controlled microneurosurgical manipulations require its precise position, because monomanual surgical manipulations may be not only non-effective, but even dangerous if occasional shift of the endoscope occurs in the surgical wound [3,7–9,11]. This necessitates use of special holder, which can provide stable position of the device in the surgical wound and permits bimanual manipulations of the surgeon and assistant. Several such systems are currently available. One of these is "Endoarm", which is routinely used at our clinic for endoscopic inspection, endoscope-assisted, and endoscope-controlled microneurosurgery. It provides excellent maneuverability within 6 degrees of freedom, smooth manipulations with avoidance of strenuous maneuvers of the surgeon, accurate fixation in any direction, and safe release, which result in high level of clinical safety of the device [13].

5 Conclusion

Using of endoscopes during surgery of vestibular schwannomas is technically feasible, effective, and safe. Endoscopic inspection allows early identification of the cranial nerves, revision of the most lateral part of the IAC for presence of the residual neoplasm, delineation of the nerve of its origin, and visualization of the non-sealed petrous bone air cells for prevention of postoperative CSF leak. Endoscope-controlled

microneurosurgical removal of the intrameatal tumors permits to attain dissection of the neoplasm from the most lateral part of the IAC. The risk of thermal injury to the cranial nerves due to use of endoscopes seems to be low. Nevertheless, special training is absolutely necessary, because endoscopic procedures are accompanied by definite learning curve. Availability of good equipment, including endoscope holder system is also very important for attainment of optimal surgical results.

References

1. McKennan KX (1993) Endoscopy of the internal auditory canal during hearing conservation acoustic tumor surgery. Am J Otol 14:259–262
2. Magnan J, Chays A, Lepetre C, et al (1994) Surgical perspectives of endoscopy of the cerebellopontine angle. Am J Otol 15:366–370
3. Rosenberg SI, Silverstein H, Willcox TO, et al (1994) Endoscopy in otology and neurootology. Am J Otol 15:168–172
4. Matula C, Tschabitscher M, Diaz Day J, et al (1995) Endoscopically assisted microneurosurgery. Acta Neurochir (Wien) 134:190–195
5. Tatagiba M, Matthies C, Samii M (1996) Microendoscopy of the internal auditory canal in vestibular schwannoma surgery: Technique application. Neurosurgery 38:737–740
6. Valtonen HJ, Poe DS, Heilman CB, et al (1997) Endoscopically assisted prevention of cerebrospinal fluid leak in suboccipital acoustic neuroma surgery. Am J Otol 18:381–385
7. Jennings CR, O'Donoghue GM (1998) Posterior fossa endoscopy. J Laryngol Otol 112:227–229
8. Goksu N, Bayazit Y, Kemaloglu Y (1999) Endoscopy of the posterior fossa and dissection of acoustic neuroma. J Neurosurg 91:776–780
9. King WA, Wackym PA (1999) Endoscope-assisted surgery for acoustic neuromas (vestibular schwannomas): Early experience using the rigid Hopkins telescope. Neurosurgery 44:1095–1102
10. Low WK (1999) Enhancing hearing preservation in endoscopic-assisted excision of acoustic neuroma via the retrosigmoid approach. J Laryngol Otol 113:973–977
11. Wackym PA, King WA, Poe DS, et al (1999) Adjunctive use of endoscopy during acoustic neuroma surgery. Laryngoscope 109:1193–1201
12. Magnan J, Barbieri M, Mora R, et al (2002) Retrosigmoid approach for small and medium-sized acoustic neuromas. Otol Neurotol 23:141–145
13. Morita A, Okada Y, Kitano M, et al (2004) Development of hybrid integrated endoscope-holder system for endoscopic microneurosurgery. Neurosurgery 55:926–932

Neuroprotective Approaches in Experimental Model of Cerebral Venous Infarct

Hiroyuki Nakase, Ryota Kimura, Toshikazu Nishioka, Ryo Tamaki, Hitoshi Miyake, Yasuhiro Takeshima, and Toshisuke Sakaki

Summary

Background and Purpose: Novel neuroprotective approaches in experimental models of cerebral venous infarct (CVI) are described.

Method and Results: We used the rat two cortical veins occlusion model. ⟨Experiment-1⟩ The rats were divided into two groups: the control and the treated group with VEGF antagonist. They were evaluated by MRI 24 h after the operation. VEGF expression was observed exclusively in the area of vasogenic edema. The both volumes of the infarction and the vasogenic edema in MRI were significantly smaller in the treated group than the control ($P < 0.05$). ⟨Experiment-2⟩ We examined sequential changes of bcl-2 family proteins and TUNEL staining in the same model. The rats were submitted to perfusion fixation at 4, 12 h and 1, 2, 4, 7 days after the vein occlusion (each $n = 4$). TUNEL positive cells began to appear at 1 day after the vein occlusion with the peak at 2 days and localized in the center and around infarction. Bax protein began to appear immunohistochemically at 4 h around the ischemic lesion, and its peak was 1 day. On the other side, bcl-2 protein was negative from the early phase to 4 days.

Conclusions: The inhibition of VEGF and apotosis might be new therapies against CVI.

Key words. cerebral venous infarction, VEGF, penumbra, rat

1 Introduction

To date the severity of the consequences of venous occlusion on the brain has been underestimated in neurosurgical practice. However, recently much attention has been paid to brain injury following cerebral venous circulation disturbances (CVCDs) as a

Department of Neurosurgery, Nara Medical University, 840 Shijo-cho, Kashihara, Nara 634-8522, Japan

result of the increasing number of neurosurgical operations for aged patients and the development of skull base neurosurgery [1–5].

We have studied experimentally on CVCDs by the rat 2 veins occlusion (2-VO) model using the photochemical thrombotic technique. The model has been developed as a good approximation of the intraoperative venous injury that might be experienced in any neurosurgical setting [6,7]. We previously demonstrated that the growth of the thrombus coincided with decrease in regional cerebral blood flow and brain damage using fluorescence angiography and cortical laser Doppler scanning in the model [8–13].

Cerebral venous disorders are potentially good outcome if diagnosed and treated promptly [2]. Therapeutic window in time and space is much wider in cerebral venous infarct (CVI) than arterial stroke. In the paper, novel neuroprotective approaches in experimental models of CVI are described.

2 Material and Methods

This animal study was conducted in accordance with the guidelines approved at the 80th general assembly of the Japan Science Council (1980).

2.1 Experiment-1

We used 25 male Wistar rats weighing 230–300 g. Spontaneous ventilation under general anesthesia was maintained during the procedures. Two adjacent cortical veins were photochemically occluded using rose bengal dye and fiberoptic illumination as described previously [6–13]. The rats were divided into two groups: the control (n = 15) and the treated group with Vascular endothelial growth factor (VEGF) antagonist (n = 10). They were evaluated by Magnetic resonance imaging (MRI) 24 h after the operation. After MRI measurements, the rats were immediately sacrificed, and the brain were served for histological and immunohistochecal analysis for VEGF [14,15].

2.2 Experiment-2

We examined sequential changes of bcl-2 family proteins and TUNEL staining in the same 2-VO model (n = 24) in rat brain. The rats were submitted to perfusion fixation at 4, 12 h and 1, 2, 4, 7 days after the vein occlusion (each n = 4). Immunohistochemical analysis of Bcl-2 family protein and TUNEL staining were performed to examine the relation with the process of cell death in the penumbra-like condition in venous circulation disorders [16].

3 Results

3.1 Experiment-1

No significant differences were observed in physiological parameters (blood PaO_2 and $PaCO_2$, mean arterial blood pressure) before and after venous occlusion and between the groups. VEGF expression was observed exclusively in the area of vasogenic edema

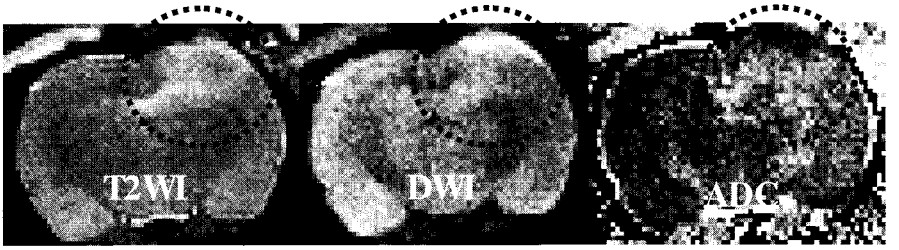


FIG. 1. Representative MRI data for the control group. The control group had large ischemic lesions and brain swelling (indicated by *black dotted circle*). The ischemic area widely extends from the surface of cortex into white matter on the T2-weighted images (T2WI). The venous infarction is detected in the cortex on the diffusion-weighted images (DWI). The brain edema, particularly vasogenic edema, is detected around the infarction and widely spreads into the white matter on the apparent diffusion coefficient (ADC) of water map [15]

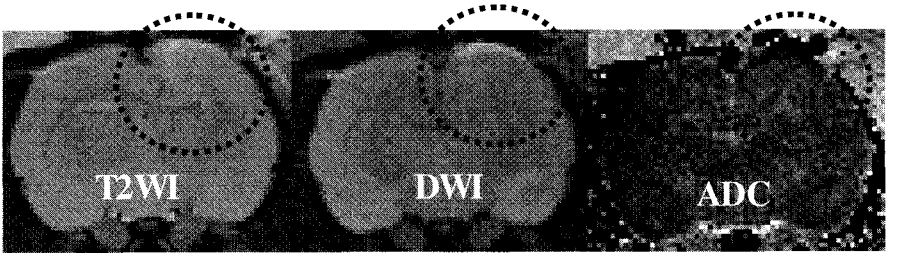


FIG. 2. Representative MRI data for the VEGF antagonist group. The antagonist group had a smaller region than the control group in all types of images [15]

which was shown as a high intensity area in apparent diffusion coefficient (ADC) map. The both volumes of the infarction and the vasogenic edema in MRI were significantly larger in the control group (Fig. 1) than the VEGF antagonist group (Fig. 2) ($P < 0.05$) [15].

3.2 Experiment-2

TUNEL positive cells began to appear at 1 day after the vein occlusion with the peak at 2 days and localized in the center and around infarction. Bax protein began to appear immunohistochemically at 4 h around the ischemic lesion. Its peak was 1 day, and they were scattered around the infarction. On the other side, bcl-2 protein was negative from the early phase to 4 days (Table 1) [16].

4 Discussion

The data in experiment-1 provide an evidence that the inhibition of VEGF attenuates vascular permeability (VP) and reduces CVI in the acute stage of cerebral venous ischemia, and the experiment-2 demonstrated that apoptosis appeared with changing depending on the time course and the space in the penumbra area of venous ischemia.

TABLE 1. Immunohistological sensitivity in penumbra area [16]

	4 h	12 h	1 day	2 days	4 days	7 days
TUNEL	−	+/−	+	++	++	+
Bax	+	+	++	++	+	+/−
Bcl-2	−	−	−	−	+/−	+

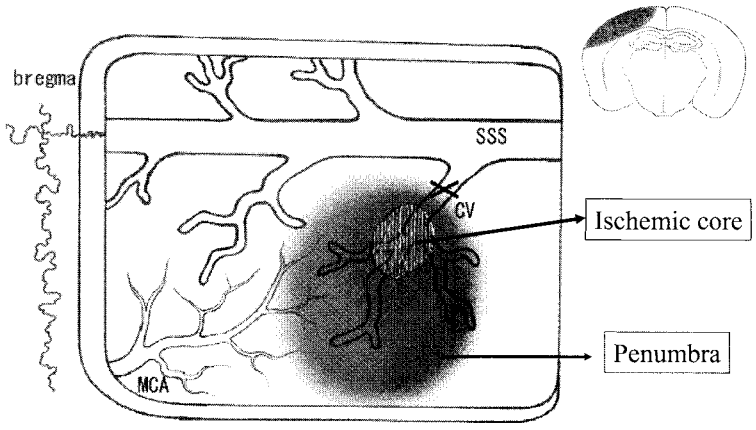


FIG. 3. Pathophysiological concept of ischemic lesion and neuronal cell death by vein occlusion. In the 2-VO model used in the experiements, the infarct (ischemic core) is small, but there is a large penumbrae with critically reduced CBF [16]

VEGF, which induces angiogenesis, is also known as VP factor. VEGF is an important angiogenesis factor, particularly in the hypoxia or ischemia induced brain damage such as strokes. However, the positive effect of the inhibition of VEGF was shown by this experiment. This is supposed to be due to the timing of the drug injection and the feature of CVI. VEGF antagonist was injected very early after occlusion and when compared to arterial ischemia, infarction maturates slowly in the model. A balanced checkpoint should exist to determine the good and/or bad effect of VEGF in the stroke [14,15].

The studies of arterial infarction using the middle cerebral artery occlusion model showed us that the apoptosis of ischemia occurred near around the infarction core, which area is becoming worth. In venous ischemia, appearance of apoptosis was observed around the ischemic center and at the distant area from the core too (Fig. 3). This area around the infarction core is incomplete ischemic stage and the function and condition of cell may be observed specific change. If the apoptosis mainly concern with venous ischemia, this programmed cell death has the time between the signal of stimulation, transportation of stimulation and appearance of cell death, and that time is useful for therapy, so that the further study is more expected [16].

In occlusive stroke, the concept of neuroprotection involved inhibition of cascade of pathological molecular events occurring under ischemia and leading to calcium

influx, activation of free radical reactions and cell death. Many neuroprotective agents have proven efficacious in animal models, but clinical trials with many agents have so far been disappointing [17]. One of the possible explanations is that the effects of neuroprotective agents on infarct size are time dependent and treatment has often been initiated much later than in successful experimental stroke model. CVI usually develops much more slowly than arterial stroke. Also, areas with moderate reduction of cerebral blood flow, penumbra, surrounding a core infarct in CVI are wider than arterial stroke. Therefore, therapeutic window in time and space is much wider in CVI. Neuroprotective candidates with the success obtained with animal models are more promising in human trial in CVI.

References

1. Nakase H, Heimann A, Kempski O (1996) Alterations of regional cerebral blood flow and tissue oxygen saturation in a rat sinus-vein thrombosis model. Stroke 27:720–727
2. Nakase H, Shin Y, Nakagawa I, et al (2005) Clinical features of postoperative cerebral venous infarction. Acta Neurochir (Wien) 147:621–626
3. Nakase H, ShinY, Fujimoto K, et al (2005) Cerebral venous ischemia by dural arteriovenous fistulas. J Stroke Cereb Dis 14(4):152–156
4. Roberson JB Jr, Brackmann DE, Fayad JN (2000) Complications of venous insufficiency after neurotologic-skull base surgery. Am J Otol 21:701–705
5. Sindou M, Auque J (2000) The intracranial venous system as a neurosurgeon's perspective. Adv Tech Stand Neurosurg 26:131–216
6. Nakase H, Heimann A, Kempski O (1996) Local cerebral blood flow in a rat cortical vein occlusion model. J Cereb Blood Flow Metab 16:720–728
7. Nakase H, Nagata K, Otsuka H, et al (1997) An experimental model of intraoperative venous injury in the rat. Skull Base Surg 7(3):123–128
8. Nakase H, Kempski O, Heimann A (1997) Microcirculation after cerebral venous occlusion as assessed by laser Doppler scanning. J Neurosurg 87:307–314
9. Nakase H, Nagata K, Otsuka H, et al (1998) Local cerebral blood flow autoregulation following asymptomatic cerebral venous occlusion in the rat. J Neurosurg 89:118–124
10. Nakase H, Nagata K, Otsuka H, et al (1998) Local cerebral blood flow autoregulation following "asymptomatic" cerebral venous occlusion in the rat. J Neurosurg 89:118–124
11. Kaido T, Nakase H, Nagata K, et al (2001) Intermittent isometric exposure prevents brain retraction injury under venous circulatory impairment. Neurol Res 23:739–744
12. Nagata K, Nakase H, Kakizaki T, et al (2000) The effect of brain compression under venous circulatory impairment. Neurol Res 22:713–720
13. Otsuka H , Nakase H, Nagata K (2000) Effect of age on cerebral venous circulation disturbances in the rat. J Neurosurg 93:298–304
14. Kimura R, Nakase H, Sakaki T, et al (2003) Vasogenic edema and VEGF expression in a rat two-vein occlusion model. Acta Neurochir Suppl 86:213–217
15. Kimura R, Nakase H, Tamaki R, et al (2005) Vascular endothelial growth factor antagonist reduces brain edema formation and venous infarction. Stroke 36:1259–1263
16. Nishioka T, Nakase H, Nakamura M, et al (2003) Apoptosis in the penumbra of vein occlusion. Jpn J Phlebol 14:275–281 (in Japanese)
17. Wahlgren NG, Ahmed N (2004) Neuroprotection in cerebral ischaemia: Facts and fancies—the need for new approaches. Cerebrovasc Dis 17:153–166

Treatment of Ruptured Intracranial Aneurysm: Our Approach

YOKO KATO[1], HIROTOSHI SANO[1], MINORU YONEDA[1], SADAYOSHI WATANABE[1], SHAMSUL ALAM[2], KHANDELWAL PRASHANT[3], SHAMSON SHARAD RAJAMANI[4], and TETSUO KANNO[1]

Summary. The question as to whether to clip or coil a specific aneurysm has been the topic of many debates and symposia. Conflicting options have been discussed over the past few years. In view of this, we decided to review our data and formulate clear indications for surgical clipping and coiling. In addition to this we wanted to study the benefits of surgical clipping for ruptured aneurysms over endovascular coiling.

We studied 450 cases, retrospectively, of ruptured cerebral aneurysms admitted to our institution from 1997 to 2003. Out of these, 324 were subjected to surgical clipping and 126 to endovascular techniques. The outcome was studied using GOS.

Of the 324 cases of surgical clipping 222 had good recovery, 38 had moderate disability, 15 had severe disability, 13 became vegetative and 36 patients died. In the endovascular group 34 had good recovery, 22 had moderate disability, 18 had severe disability, 15 became vegetative and 37 patients died. Grade to Outcome was compared in both the forms of treatment. In our series clipping for ruptured aneurysm was preferred to coiling in fusiform shape aneurysms, large or giant aneurysms, MCA aneurysms, blister aneurysms, complex configurations, partially thrombosed aneurysms and aneurysms associated with intracranial hemorrhage. Coiling was performed for basilar tip and trunk aneurysms, high anterior communicating artery aneurysms, patients with subacute stage of sub-arachnoid hemorrhage, and those with associated medical complications.

Based on this study we were able to coin a few definite indications for clipping, even in the times of advanced endovascular techniques. In addition we could also prove benefits of surgical clipping over endovascular technique in severe sub-arachnoid hemorrhage.

Key words. subarachnoid hemorrhage, aneurysms, treatment

[1] Department of Neurosurgery, Fujita Health University Hospital, Toyoake, Aichi, Japan, [2] Department of Neurosurgery, Bangabandhu Sheikh Mujib Medical University, Shahbag, Dhaka, Bangladesh, [3] Department of Neurosurgery, KEM Hospital, Seth G.S. Medical College, Mumbai, India, and [4] Department of Neurosurgery, Pondicherry Institute of Medical Sciences, Pondicherry, India

1 Introduction

There have been revolutionary developments in surgical clipping and endovascular coiling for the treatment of ruptured aneurysms. Surgical clipping as a treatment modality has been developed since the past 100 years. Endovascular coiling of intracranial aneurysms is a technique that has been available for the past 10 years and widely accepted throughout the world. Guglielmi detachable coil treatment is becoming an accepted alternative to microsurgical clipping for select intracranial aneurysms. Since its development a number of publications have demonstrated that endovascular treatment may be effective in reducing rebleeding after subarachnoid hemorrhage due to aneurysmal rupture [1–3]. Although it is more comfortable for the patients and is often associated with lower complications rate, coiling is not thought to be resolve all the mass effect caused by aneurysms. Typically the only questions asked about aneurysm therapy are the ability to close and maintain closure of the aneurysm and the patients does not die or sustain a major complication of treatment. The question as to whether to clip or coil a specific aneurysm has been the topic of many debates and symposia. Conflicting reports have been presented to us over the past few years [2,4–6]. Many factors must be considered when determining whether to coil or clip. Dr. Jeffrey Stone, an interventional neuroradiologist at the MCG Neuroscience Center, warns that coiling is not necessarily less risky than clipping—just less invasive. MCG Neuroscience Center physicians do not view the two procedures as competitors [7]. Patients with aneurysms, whether ruptured or not, are assessed by a multidisciplinary team that recommends the procedure deemed most effective for each individual case. Patients of ruptured aneurysms would benefit maximally from this healthy competition between clipping and coiling. ISAT (International Subarachonoid Aneurysm Treatment Trail) has shown that, in those patients with aneurysms 10 mm or less in size that have a favorable configuration to be coiled, coiling is associated with less morbidity than clipping, Dr. Britz wrote. "However, this finding cannot be translated into believing that coiling is safer than clipping in all cerebral aneurysms." He noted that under current practice most middle cerebral artery aneurysms are treated better with clipping than with coiling. In addition, some aneurysms, such as those with a small dome-to-neck ratio or those that have branches coming out of the aneurysm itself have a worse outcome with coiling [7]. We decided to review our data and formulate clear indications for surgical clipping and coiling. In addition to this we studied the benefits of surgical clipping for ruptured aneurysms over endovascular coiling.

2 Material and Methods

We studied 450 cases of ruptured cerebral aneurysms admitted to our institution from 1997 to 2003. Of these patients, 324 were subjected to surgical clipping and 126 were treated by endovascular techniques. Treatment guidelines were selected on the basis of the Hunt and Kosnik grade at the time of admission, age of the patient and morphology of the aneurysm. 3D CT and MR images were obtained in each case apart from the routine scans and the clinico-radiological findings were discussed together by the senior experts in Neurosurgery and Interventional Endovascular surgery.

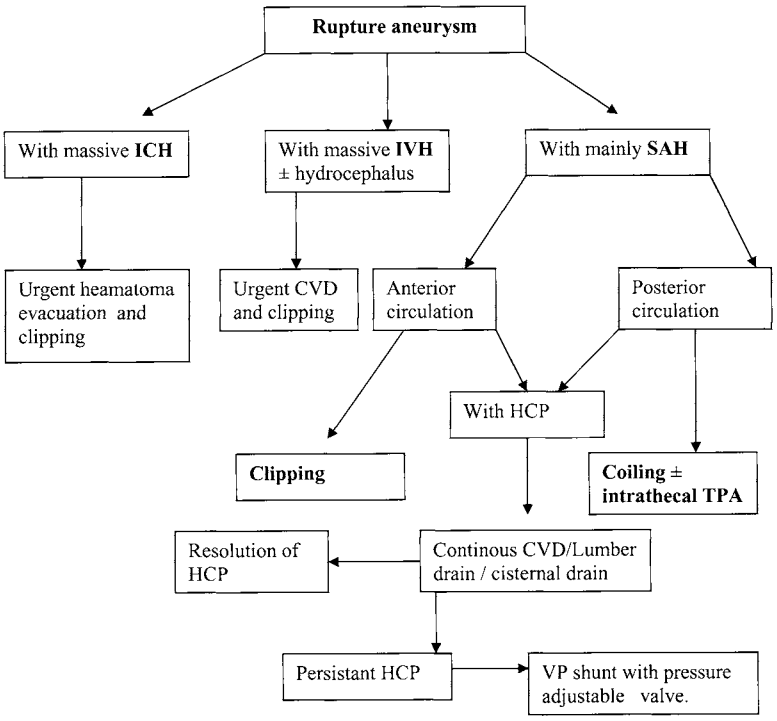


FIG. 1. Flow diagram of the management plan admitted with rupture aneurysm. *ICH*, Intracerebral heamatoma; *IVH*, Intraventricular haematoma; *CVD*, Continuous ventricular drainage

Surgery was performed in patients with HK grade 0–3, grade 4 (GCS 9–12), grade 5 (with hydrocephalous or intracerebral hematoma) and those who presented in an acute setting (0–3 days). Endovascular therapy was selected for those patients who presented in a sub-acute stage (4–14 days of vasospasm) or with HK grade 4 (GCS 7,8) or grade 5 (without hydrocephalous or intracerebral hematoma), age more than 70 and for those located in the posterior circulation. Surgical treatment consisted of clipping with or without ventricular drainage. It was performed by a standard free flap pterional craniotomy (Yasargil method) or subocciptal craniectomy as the case demanded. Endovascular therapy compromised of GDC coiling, CSF wash out with urokinase and or TPA (Fig. 1). The outcome was evaluated using GOS at the time of discharge from the hospital.

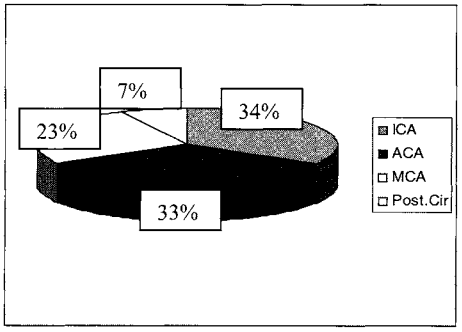


FIG. 2. Location of aneurysms treated by clipping

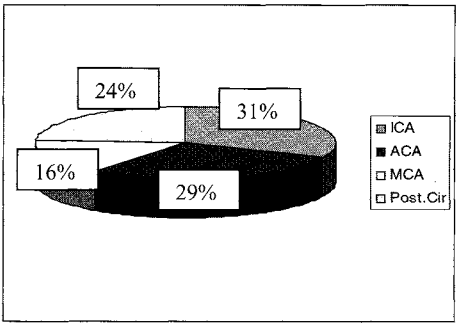


FIG. 3. Location of aneurysms treated by coiling

3 Results

Of the 324 patients treated by surgical clipping, 110 were located on ICA, 106 on ACA, 85 on MCA and 23 in Posterior circulation, while in the endovascular group the distribution was 40, 36, 20 and 30 respectively (Figs 2,3). 389 patients had single aneurysm whereas 61 belonged to the multiple constellation.

In the surgical group 28 patients had presented in Grade I, 76 in Grade II, 118 in Grade III, 57 in Grade IV and 45 in Grade V (Hunt and Kosnik grade), while in the group treated by endovascular techniques, the distribution was 7, 27, 17, 32, and 43 in the respective grades. In the surgical group, 222 patients had good recovery, 38 patients had moderate disability, 15 patients had severe disability, 13 patients became vegetative and 36 patients died. In the endovascular group 34 patients had a good recovery, 22 patients had moderate disability, 18 patients had severe disability, 15 patients became vegetative and 37 patients died. Grade to Outcome was compared in both the forms of treatment (Tables 1,2).

4 Discussion

Optimal treatment for ruptured aneurysms must demonstrate the following features: first, the highest rate of complete occlusion; second, the lowest complication rate, and the cost effectiveness. So, what would be the best treatment option for each aneurysm

TABLE 1. Grade to outcome in patients with operative treatment

Clipping	Gr I	Gr II	Gr III	Gr IV	Gr V	Total
GR	24	69	92	28	9	222
MD	3	4	11	15	5	38
SD	0	1	5	3	6	15
V	0	0	3	5	5	13
D	1	2	7	6	20	36
Total	28	76	118	57	45	324

TABLE 2. Grade to outcome in patients with endovascular treatment

Coiling	Gr I	Gr II	Gr III	Gr IV	Gr V	Total
GR	6	16	0	6	6	34
MD	1	7	5	7	2	22
SD	0	2	4	9	3	18
V	0	0	3	3	9	15
D	0	2	5	7	23	37
Total	7	27	17	32	43	126

type? Since open surgery for intracranial aneurysm began to be used, aneurysms of the posterior circulation, particularly aneurysms of the basilar trunk, appeared more difficult to treat than aneurysms of the anterior circulation [7]. This lead to coil embolization being recommended more commonly for posterior circulation aneurysms. Other aspects supporting this recommendation included: an easier access to the vertebro-basilar system by the endovascular approach; better results for basilar artery apex aneurysms treated by coil embolization [8,9]; and coil embolization being associated with low failure rates for these aneurysms [10]. Currently, in the most experienced group performing coil embolization, posterior circulation aneurysms are more commonly treated by embolization than by standard open surgery [11].

In literature, surgery for ruptured aneurysms within the first 72 h, was found to be more difficult and associated with higher operative morbidity compared with a delayed procedure [12] or surgical clipping of an unruptured aneurysm [10,13]. Surgical clipping, therefore, appears to be the best treatment to recommend for anterior circulation aneurysms, in particular the middle cerebral artery aneurysms, complex aneurysms and Giant aneurysms [14–16].

In our series clipping for ruptured aneurysm was preffered over coiling in fusiform aneurysms, large or giant aneurysms, MCA aneurysms, blister aneurysms, complex configurations, partially thrombosed aneurysms and aneurysms associated with intracerebral hemorrhage.

Coiling was preferred for basilar tip and trunk aneurysms, high anterior communicating artery aneurysms, patients with subacute stage of sub-arachnoid hemorrhage, and those with associated medical complications.

Raftopoulos [10] considered that surgical clipping was more effective and safer than coil embolization for anterior circulation aneurysm, even for more complex aneurysms. David et al [4] in their data confirmed the long term efficacy of aneurysm

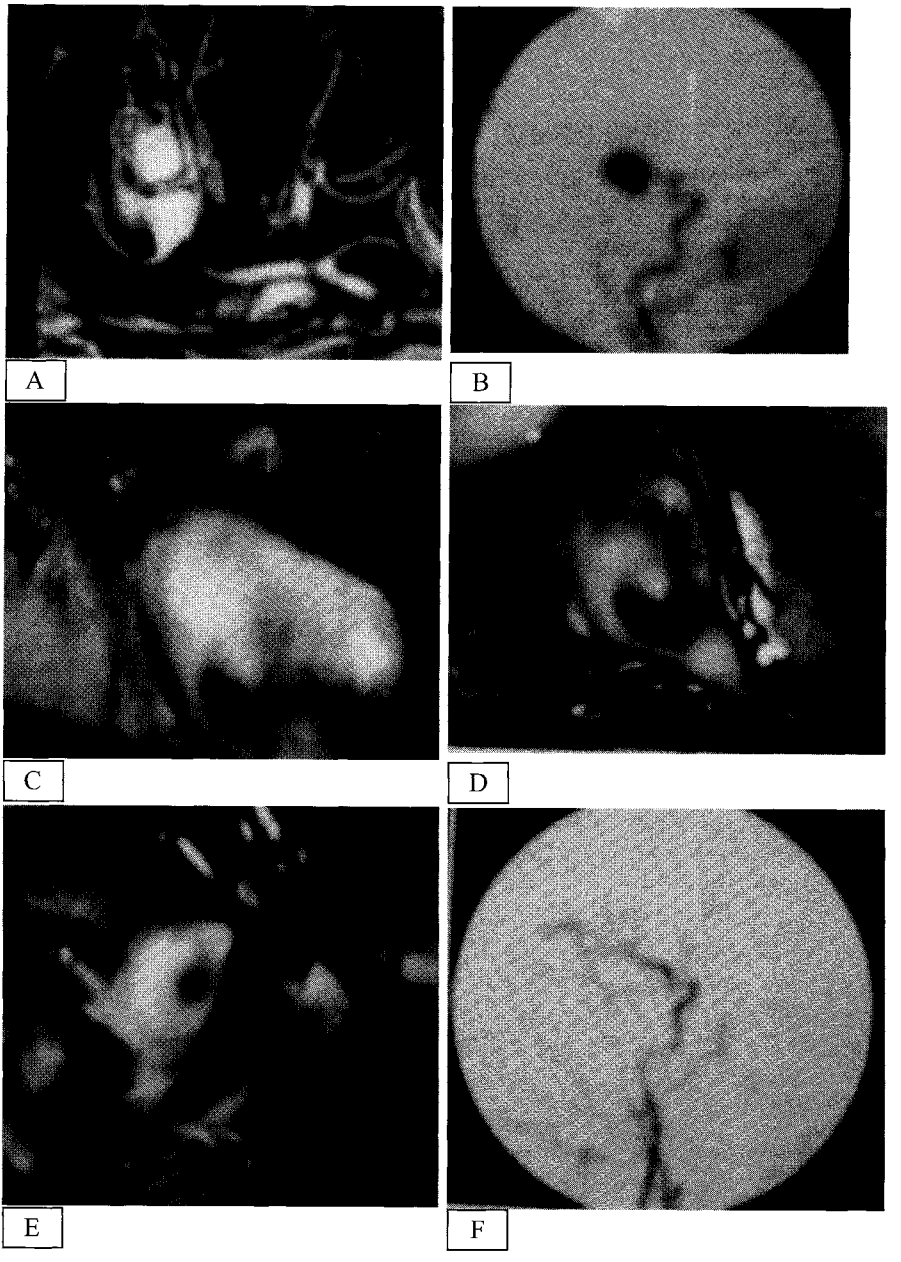


FIG. 4. A patient of middle cerebral artery aneurysm presented with grade-1 subareachnoid haemorrhage. **A** 3D CT scan and **B** DSA done revealed a giant aneurysm of the MCA bifurcation. He was subjected to microsurgery. **C** Intraoperatrively the aneurysm neck was found to be atherosclerotic with thickened walls. **D,E** The aneurysm was clipped with the help of 2 clips. **F** Postoperative angiogram revealed complete obliteration of the aneurysm

clip ligation with a 98.5% permanent obliteration rate. However other authors report that coil embolization gave better results than the best surgical series [2,3,17]. The short term results of the first randomized trail comparing interventional and surgical treatment of aneurysms, the international subarachonoid aneurysm treatment trail (ISAT), has recently been published and speaks in favour of endovascular coiling, although controversial opinions are heard. Later, the International Subarachnoid Aneurysm Trial (ISAT) also showed for ruptured intracranial aneurysms a difference in favour of coil embolization [5]. There was a definite bias in this study, due to the exclusion of major vascular neurosurgical clipping centres in the United States and Japan.

In a recent study by Raymond et al, long term follow up was obtained in 55% of 501 aneurysms treated by coiling over a 10 year interval from 1992–2002. Recurrence was identified in 33.6% of the total number of aneurysm followed. Major recurrences were identified in 20.7% of the patients and appeared at a mean interval of 16.49 ± 15.93 months. In fact in their total number of 501 patients only 35.9% were treated with what was defined as complete occlusion. In 46.3% there were residual neck, in 13.8% there was residual aneurysm, and in 4% there was failure to place coil. Raymond et al, defined a 0.8% bleeding rate in clinical follow up interval of 31.32 months.

In our series severe grade acute sub-arachnoid hemorrhage showed a better outcome than coiling as against ISAT. This disparity between ISAT and our series, with respect to severe sub-arachnoid hemorrhage could be due to following reasons [18].

(1) Treatment in the clipping group of ISAT was initiated by 3.7 days, whereas, coiling cases, by 3.1 days. This lapse of 14 h in the acute stage was an important factor missing out on the golden hour.
(2) Most of the patients among the 2143 ISAT cases were in better grades (1 or 2), where satisfactory results are expected.
(3) The cases which were excluded comprised of more clipping cases than coiling.
(4) Patients with Middle cerebral and Posterior circulation aneurysms were nearly excluded (97.3% of cases; anterior circulation aneurysms).
(5) In the ISAT study the rate of heaemorrhage in coiled patients from time of treatment to 1 year was reported as 3.2% and in the clipped patients 1.3%.
(6) Lower level of sub-specialization in the neurosurgical group existed, in addition to the absence of long-term evaluation of coil embolization.

In our series we found that clipping had definite advantages over coiling, such as:

(1) 3D CT angiogram [19] was enough to plan surgery reducing the time to surgery and also being cost-effective. A repeat DSA was also not required postoperatively.
(2) Site of aneurysm was seldom a limiting factor.
(3) There were no problems of coil compaction or thromboembolic episodes.
(4) An additional treatment incidence was less.
(5) Hematoma reduction aided resolution of brain injury and reduced vasospasm.
(6) Simultaneous treatment of hydrocephalous by procedures like lamina terminalis fenestration etc could be performed.

Endovascular coiling has certain advantages such as minimal invasiveness, no brain manipulation, reduction of vasospasm, and lesser hospital stay, but it did not outweigh its limitations as outlined above. Several authors stress the potential advantages of coil

embolization in select patients over surgery in terms of cognitive outcome especially ruptures ACOM aneurysm. It is well known that when coiling of an aneurysm, much of the risk of thromboembolic complications or parent vessel occlusion. Coiling prevents the majority of acute rehaemorrhage form ruptured aneurysm, however clipping reduces rebleeding by more than 50% compared with endovascular coiling but incidence of seizure is more then coiling.

Dr. Britz wrote. "Each patient and their aneurysm is different and the decision has to be made about what is in the best interest for each patient. None of the treatment options are superior, but rather each has strengths and weaknesses that can be used to decide what is best for each patient. Some patients should be clipped and some should be coiled." [7]

5 Conclusion

In our series, microsurgical clipping had a more favourable outcome than endovascular coiling in acute severe sub-arachnoid hemorrhage cases as oppose to the ISAT studies. In spite of advances in the coiling technique and it being a less morbid procedure, there are certain limitations and disadvantages. Appropriate selection is important prior to allocating the treatment strategy in each case of severe subarachnoid hemorrhage. We recommend that, for most posterior circulation intracranial aneurysms, coil embolization appears to be the procedure of choice while the vascular neurosurgeon should clip anterior circulation aneurysms, large or giant aneurysms, complex aneurysms and aneurysms situated on the middle cerebral artery. Evolving endovascular technology should be integrated with the microsurgical management of aneurysms in the event of failure of a single conventional modality.

References

1. Byrne JV, Sohn MJ, Molyneux AJ, et al (1999) Five-year experience in using coil embolization for ruptured intracranial aneurysms: Outcomes and incidence of late rebleeding. *J Neurosurg* 90:656–663
2. Raymond J, Roy D (1997) Safety and efficacy of endovascular treatment of acutely ruptured aneurysms. *Neurosurgery* 41:1235–1245
3. Vinuela F, Duckwiler G, Mawad M (1997) Guglielmi detachable coil embolization of acute intracranial aneurysm: Perioperative anatomical and clinical outcome in 403 patients. *J Neurosurg* 86:475–482
4. David CA, Vishteh AG, Spetzler RF, et al (1999) Late angiographic follow-up review of surgically treated aneurysms. *J Neurosurg* 91:396–401
5. International Subarachnoid Aneurysm Trial (ISAT) Collaborative Group (2002) International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: A randomized trial. *Lancet* 360:1267–1274
6. Raymond J, Guilbert F, Weill A, et al (2003) Long-term angiographic recurrences after selective endovascular treatment of aneurysms with detachable coils. *Stroke* 34: 1398–1403
7. Osterweil N (2005) Coils provide survival advantage in ruptured brain aneurysms. *MedPage Today*, September 01, 2005

8. Gruber DP, Zimmerman GA, Tomsick TA, et al (1999) A comparison between endovascular and surgical management of basilar artery apex aneurysms. *J Neurosurg* 90:868–874
9. Tateshima S, Murayama Y, Gobin YP, et al (2000) Endovascular treatment of basilar tip aneurysms using Guglielmi detachable coils: Anatomic and clinical outcomes in 73 patients from a single institution. *Neurosurgery* 47:1332–1339
10. Raftopoulos C ((2005) Is surgical clipping becoming underused? *Acta Neurochir (Wien)* 147:117–124
11. Murayama Y, Nien YL, Duckwiler G, et al (2003) Guglielmi detachable coil embolization of cerebral aneurysms: 11 years' experience. *J Neurosurg* 98:959–966
12. Seifert V, Stolke D, Trost HA (1988) Timing of aneurysm surgery. Comparison of results of early and delayed surgical intervention. *Eur Arch Psychiatr Neurol Sci* 237:291–297
13. Orz YI, Hongo K, Tanaka Y, et al (2000) Risks of surgery for patients with unnruptured intracranial aneurysms. *Surg Neurol* 53:21–27
14. Drake CG, Peerless J (1997) Giant fusiform intracranial aneurysms: Review of 120 patients treated surgically from 1965 to 1992. *J Neurosurg* 87:141–62
15. Lawton T, Spetzler RF (1995) Surgical management of giant intracranial aneurysm: Experience with 171 patients. *Clin Neurosurg* 42:245–66
16. Sano H, Kato Y, Shankar K, et al (1998) Treatment and results of partially thrombosed giant aneurysms. *Neurol Med Chir (Tokyo)* 38 (Suppl.):58–61
17. Lot G, Houdart E, Cophignon J, et al (1999) Combined management of intracranial aneurysms by surgical and endovascular treatment. Modalities and results from a series of 395 cases. *Acta Neurochir (Wien)* 141:557–562
18. Christopher S, Ogilvy MD (2003) Neurosurgical clipping versus endovascular coiling of patients with ruptured intracranial aneurysms. Stroke 34:2540
19. Kato Y, Sano M, Katada K, et al (1998) Clinical usefulness of 3D CT endoscopic imaging of cerebral aneurysms. *Neurology India* 46 (Suppl.):56

Endoscopic Endonasal Transsphenoidal Surgery for Pituitary Macroadenoma

SURESH K. SANKHLA

1 Introduction

The endoscopic endonasal transsphenoidal approach is a minimally invasive surgical technique for the removal of pituitary adenomas. This technique has several well-known advantages over the standard microsurgical transsphenoidal operation (Table 1). We report our experience with this technique in the surgical management of patients with pituitary macroadenoma and highlight few technical points that make this technique extremely useful and versatile.

2 Methods & Results

Forty-three patients with pituitary macroadenoma, including 7 with residual or recurrent tumors, were operated on using this approach in last 4 years (Tables 2,3). There were 24 non-secreting, 10 GH-secreting, and 9 PRL-secreting adenomas. The tumor removal was gross-total in 29 (67%), subtotal in 11 (26%), and partial in 3 (7%) patients (Table 4 and Figs. 1–3). Complications including CSF leakage and transient diabetes insipidus were observed in 9% of patients (Table 5). There was no death or serious morbidity related to this procedure.

3 Discussion

The endoscope significantly adds to the versality of the transsphenoidal approach used for the lesions in and around the sella. Because the endoscope is placed closer to the sella, more convenient regular straight microsurgical instruments, which are generally unsuitable for the standard microscopic approach, can be used comfortably with this approach (Fig. 4). With angled 30-degree and 45-degree endoscopes, it is possible to examine the entire sellar and suprasellar regions more closely (Fig. 5). Tumor remnants in the lateral recesses, often missed by the microscopic vision can be

B. Nanavati Hospital and Medical Research Centre, A-503, Chaitanya Towers, Appasaheb Marathe Road, Prabhadevi, Mumbai 400 025, India

ADVANTAGES

Endoscopic *v/s* microscopic surgery

- No nasal/oral incision
- No nasal speculum
- Excellent illumination
- No nasal packing
- No postop. epistaxis, lip anesthesia, deviated nasal septum
- Shorter operative time
- Reduced hospital stay

TABLE 1

PITUITARY MACROADENOMA (2000–2004)

Total no. of pts.	43 (F = 25; M = 18)
Non-secreting	26
GH-secreting	10
PRL-secreting	7

TABLE 2

CLINICAL FEATURES

Headache	38
Visual disturbances	24
CN palsy	6
Acromegaly	10
A/G	16
Infertility	3

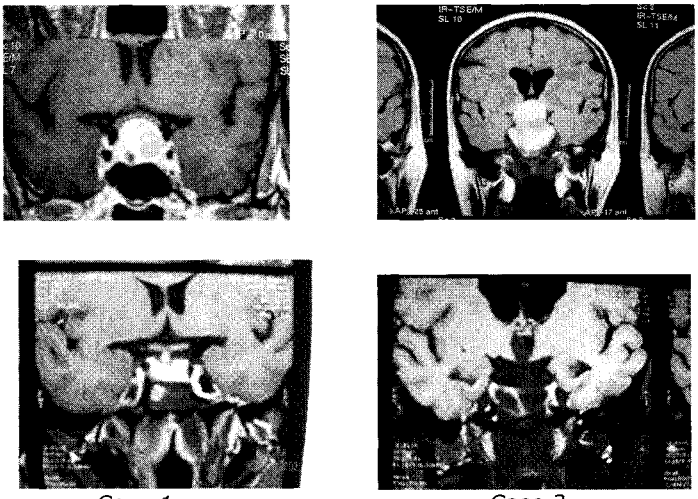
TABLE 3

RESULTS

Tumor Removal	No. of Patients	%
Gross total	29	67%
Subtotal	11	26%
Partial	3	7%

TABLE 4

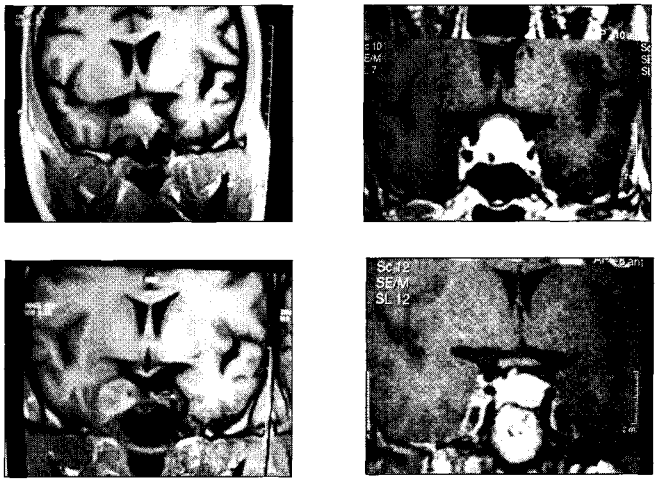
TOTAL TUMOR REMOVAL



Case 1 Case 2

FIG. 1

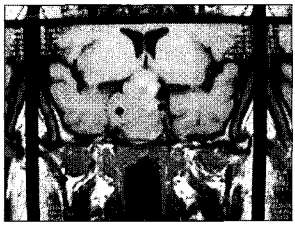
SUBTOTAL REMOVAL



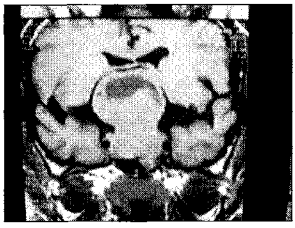
Case 3 Case 4

FIG. 2

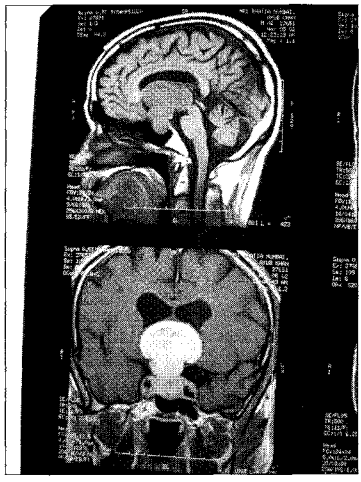
PARTIAL REMOVAL



Case 5



Case 6



Case 7

FIG. 3

COMPLICATIONS

Nasal bleeding	1
CSF leak	8
•Intraoperative	6
•Postop. CSF rhinorrhea	2
Meningitis	1
Transient DI	8
Endo. disturbances	0
Intracranial hematoma	0
Visual complications	0

TABLE 5

ADVANTAGES (I)

Regular microsurgical instruments can be used

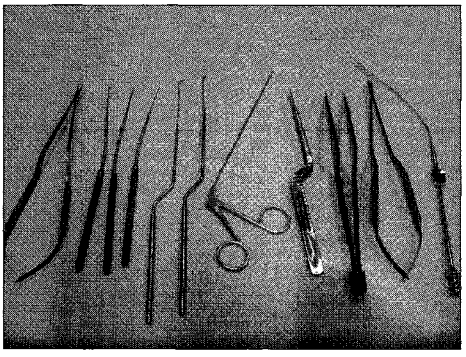
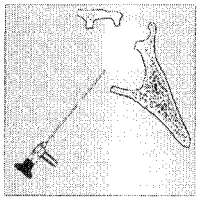


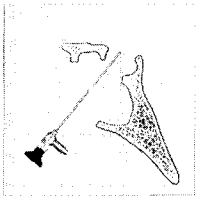
FIG. 4

ADVANTAGES (II)

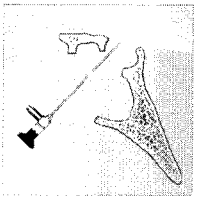
Wider view of the intrasellar & suprasellar anatomy can be obtained



0^0 Endoscope



30^0 Endoscope



45^0 Endoscope

FIG. 5

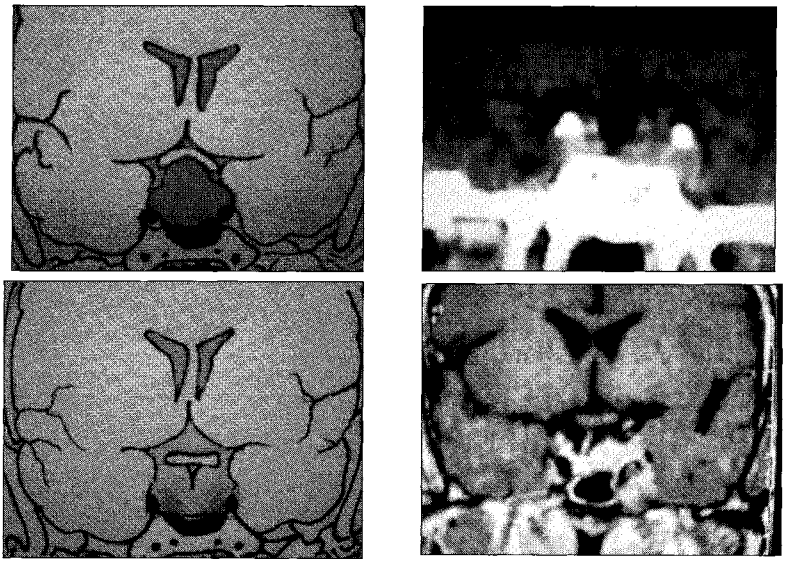


FIG. 6

identified and removed easily with safety. Uniform tumor decompression using endoscopic technique prevents central prolapse of the suprasellar cistern and redundant diaphragm into the sellar cavity, and thus, minimizes obscuration of the residual tumor in the lateral recesses (Fig. 6).

4 Conclusion

Endonasal endoscopic transsphenoidal surgery is a minimally invasive technique. The approach is safe and more versatile, and has definite advantages over the standard microsurgical transsphenoidal technique. The incidence of surgical trauma and procedure-related complications are minimal, and the procedure is better tolerated by patients.

Microsurgical Treatment of Posterior Cranial Fossa Tumors Via Keyhole Approaches

Qing Lan, Zhigang Gong, Zhiyuan Qian, Jian Chen, Shihai Liu, Zhaohui Lu, and Qiang Huang

Summary

Objective: To explore the surgical outcome and skills of keyhole approaches to posterior cranial fossa tumors.

Methods: A retrospective analysis of the clinical data of 43 consecutive patients with posterior cranial fossa tumors, including acoustic neurinomas, petroclival meningiomas, pontine tumors, fourth ventricular tumors, etc. was conducted. The subtemporal, retromastoid, or middle suboccipital keyhole approach was chosen according to the anatomic positions of those different tumors. The length of the incision was about 4 cm, and the diameter of the bone window was 2.0–2.5 cm. Normally dura was sutured tightly and no catheter was placed in the operative fields.

Results: The tumors were totally removed in 37 of the 43 patients (86.0%), subtotally removed in 5 (11.6%) and mostly removed in 1 (2.3%). There were no complications obviously associated with the limited exposure resulting from keyhole approaches.

Conclusion: Microsurgical treatment of posterior cranial fossa tumors via keyhole approaches, with the safe, succinct and minimally invasive property, is one of the promising directions in modern neurosurgery.

Key words. neurosurgical procedure, cranial fossa, posterior, microsurgery, keyhole

1 Introduction

The neurosurgical keyhole operation which is a new concept developed recently, especially characterized by the supraorbital subfrontal eyebrow approach, has be widely applied for intracranial tumors and aneurysms [1–3]. However, big craniotomies with large incisions are still predominant in the surgical treatments of posterior cranial

Department of Neurosurgery, Second Affiliated Hospital of Soochow University, 1055 Sanxiang Road, Suzhou 215004, Jiangsu, China

fossa lesions. There are few reports about modern keyhole techniques used in this field, although the retromastoid approach applied for decades in the treatment of trigeminal neuralgia, in a sense, may be considered as one minimally invasive keyhole approach. Based on the rationale of modern keyhole techniques, this approach has been developed for intracranial neoplasms. Here the therapeutic effects of various posterior fossa keyhole approaches tried in our preliminary study were analyzed retrospectively and reported in detail.

2 Clinical Material and Methods

2.1 Clinical Material

Between August 2000 and June 2004, 43 consecutive patients (22 males and 21 females) with posterior cranial fossa tumors were admitted at our department. The patients' age ranged from 3 to 73 years with a mean age of 47.5 years. The distribution of tumors in this study is illustrated in Table 1. All these tumors were detected by the preoperative magnetic resonance images, removed via keyhole operations, and verified by histopathological findings.

2.2 Methods

2.2.1 Surgical Approaches

According to the different anatomic features and different characteristics of the tumors, different surgical approaches were selected and modified individually, including the subtemporal keyhole approach, the retromastoid keyhole approach and the middle suboccipital keyhole approach (Table 1). No additional expansion of the incisions and the bone windows was needed to be performed intraoperatively.

2.2.2 Surgical Methods

All the skin incisions were linear, about 4 cm in length. In the subtemporal keyhole approach, a small bone flap was cut with a craniotome. This flap was replaced and secured after surgery, while in the other keyhole approaches the bones were simply removed with a high-speed nitrogen-driven drill to make suitable bone windows approximately 2.0–2.5 cm in diameter. At the end of the operation the dura was sutured watertightly, with no epidural or subdural drainage placed.

Subtemporal Keyhole Approach [1]

The patient was placed supine, and his ipsilateral shoulder was elevated 10 to 15 degrees with a cushion beneath, so that the contralateral carotid artery and the internal jugular vein were not impacted. Furthermore, according to the lesion position, the head was rotated 45 to 80 degrees contralaterally to keep the zygomatic arch horizontal to the floor. Then the head was retroflexed 10 to 15 degrees, in order not to oppress the trachea. Subsequently, the head was bended 15 to 20 degrees laterally toward the contrary side, supplying surgeons a comfortable posture for operation. In this head position the temporal robe was automatically detached downward from the skull due to the gravitation, which reduced the need of intraoperative retraction. The

TABLE 1. Tumor distribution and relative keyhole approaches in this study

Location	Pathology	No. of cases	Keyhole approaches (cases)		
			Subtemporal	Retromastoid	Middle suboccipital
Cerebellopontine angle (CPA)	Acoustic neurinoma	18		18	
	Meningioma	1		1	
	Ependymoma	1		1	
Petroclival region	Meningioma	8	6	2	
Pons	Glioma	3	1	2	
	Metastasis	2	1		1
	Gliosis	1			1
Fourth Ventricle	Medulloblastoma	2			2
	Ependymoma	2			2
Cerebellar hemisphere	Metastasis	2		1	1
	Hemangioblastoma	1			1
Free margin of the tentorium	Meningioma	1		1	
Foramen magnum-sellar region-CPA	Cholesteatoma	1		1	

hair before the ear was shaved within a range of 1.5 cm × 5.0 cm. Inside this area, a vertical linear epifascial skin incision, approximately 4 cm in length, was created upward from the superior margin of the zygomatic arch. After the skin was opened, the subcutaneous structure was dissected meticulously, so that usually the superficial temporal artery could be kept intact. Exposed by a Weitlaner retractor, the temporal muscle fascia was incised in a Y-shaped fashion with an electrocautery. The lower border of the temporal muscle was then bluntly separated and retracted upward, exposing the squamous bone. If the muscle was thick, a tiny vertical incision at the posterior portion of the temporal muscle may allow better exposure of the temporal bone. After the muscle was retracted bilaterally, a burr hole was placed on the bone. Then a bone flap (2.0–2.5 cm in diameter) was removed with a craniotome. The temporal bone was further drilled from the lower rim of the bone window to the bottom of the middle fossa. Normally, the diameter of this bone window was about 2.5 cm, and the posterior rim of this window was approximately 1 cm anterior to the external auditory meatus. During this procedure, care was taken not to damage the branches of the facial nerve running underneath the zygomatic arch. The temporal dura was incised in a valve shape and reflected basally. The temporal lobe was elevated gently with a spatula. And the cerebrospinal fluid (CSF) was aspirated carefully to reduce the intracranial pressure (ICP) gradually. Then the ambient cistern could be accessed and dissected carefully.

Retromastoid Keyhole Approach

A prone-oblique position was used. The head which faced down first was later rotated 20 to 30 degrees toward the contrary side, in order to supply a favorable straight viewing angle. In this case, the cerebellar hemisphere could be retracted not too much, and the cerebellopontine cistern could also be opened smoothly. Furthermore, according to the lesion location, the head position could be adjusted freely intraoperatively by tilting the operation bed toward the left side or the right side. A 4 cm linear incision was designed, which was approximately 2 cm medial to the mastoid process. The upper end of this incision arose from the conjunction line of the inion and the basal portion of the mastoid process. After the skin was opened, the subcutaneous tissue and the occipital muscle were dissected with an electrocautery. The musculature was retracted bilaterally with two Weitlaner retractors to expose the occipital bone. A burr hole posteromedial to the mastoid process was made with the high-speed bone drill. This burr hole was further expanded, with the drill, to a bone window about 2 cm in diameter. The upper rim of this window was near the inferior margin of the transverse sinus. After a small base portion of the mastoid process was removed, the lateral rim of this bone window reached the posterior margin of the sigmoid sinus. If the mastoid air cells were opened, bone wax was required to occlude them. If need, the inner layer of the bone window could also be drilled to expand the field of view. The dura was also incised in a valve fashion and reflected laterally toward the sigmoid sinus. Afterwards, the lateral portion of the cerebellar hemisphere was elevated gently with a retractor, and the CSF was aspirated simultaneously to reduce the ICP gradually. Furthermore, the cerebellopontine cistern was opened to release more CSF. If the mass in the cerebellopontine angle (CPA) was so big that there was little CSF able to be removed, the inferolateral portion of the cerebellar hemisphere could be elevated with a retractor blade to dissect the cisterna magna for the alternative drainage of the

CSF. When the cisterns were opened, the arachnoid membrane should be dissected along the surface of the cerebellar hemisphere to avoid the possible injury of vital structures such as the lower cranial nerves, the facial nerve, the acoustic nerve and so on. If preoperative images showed the tumor was giant, which implied intraoperative aspiration of CSF would be very difficult, a lumbar drain was suggested to be placed preoperatively for intraoperative CSF release before dissecting the tumor.

Middle Suboccipital Keyhole Approach

The patient was placed in the lateral oblique position, with the head and breast elevated 20 to 30 degrees. Moreover, the head was flexed anteriorly about 30 degrees to create a good viewing angle for surgery. A middle skin incision was designed, the lower end of which was approximately 1 cm inferior to the foramen magnum. This incision extended upward for about 4 cm along the midline. After the skin was incised, the subcutaneous tissue and the median avascular plane was then dissected with the aid of a electrocautery. The operative field was exposed well with two Weitlaner retractors. Furthermore, with a drill, a bone window (about 2 cm in diameter) was created, superior to the foramen magnum. The dura was opened in a Y fashion, and the dura edges were tented superiorly and laterally. The cisterna magna was opened to release the CSF. After the cerebellar tonsils were retracted bilaterally, the whole fourth ventricle was exposed meticulously.

2.2.3 Postoperative Evaluation

On 1–3 days postoperatively, the magnetic resonance imaging was performed on every patient to evaluate the tumor resection.

3 Results

In this study, tumors were totally removed in 37 out of 43 patients (86.0%), subtotally removed in 5 (11.6%) and mostly removed in 1 (2.3%).

As to the diameters of the 18 acoustic neurinomas, one was smaller than 3 cm, while 4 between 3–4 cm, 8 between 4–5 cm and 5 bigger than 5 cm. All these acoustic neurinomas were totally resected via the retromastoid keyhole approach, and the facial nerves were preserved in 83.3% (15/18). A typical case is presented in Fig 1. However one patient died 3 days postoperatively, due to subsequent brain stem edema.

There were 8 meningiomas located in the petroclival regions, and the longest diameters of these tumors ranged form 3.0 cm to 5.0 cm. By use of the subtemporal keyhole approach in 6 cases and the retromastoid keyhole approach in 2 cases, 5 meningiomas were totally removed (62.5%), while 2 were subtotally removed (25%) and 1 was grossly removed (12.5%). Postoperatively 2 patient remained hemiparesis and 1 patient had mild facial nerve paralysis. One typical case is presented in Fig. 2.

Among the six patients with pontine neoplasms, 2 accepted the subtemporal approach, 2 accepted the retromastoid keyhole approach and the other 2 accepted the middle suboccipital keyhole approach. Three tumors were resected completely and the other three tumors were subtotally resected. There were no neurological deficits in these patients. However, in one patient with the subtemporal keyhole approach, due to the intraoperative removal of the petrous apex, cerebrospinal fluid otorrhea occurred, which was revised later via the same approach.

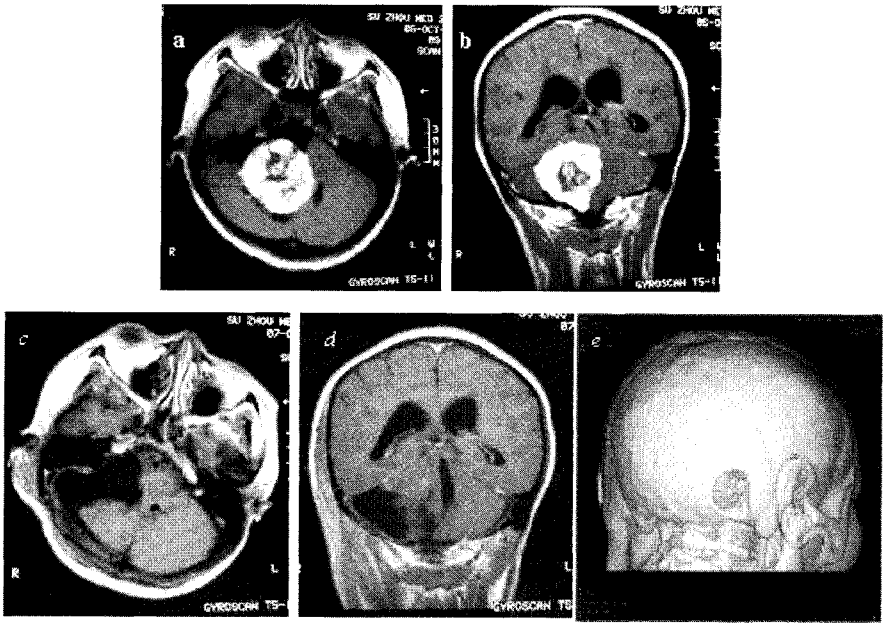


FIG. 1. The preoperative and postoperative images of one patient with right acoustic neurinoma resected via a retromastoid keyhole approach. **a, b** Preoperative MRI; **c, d** MRI on the fist postoperative day; **e** The skull demonstrated by the reconstructed 3D-CT obtained one week postoperatively

As for the 4 tumors in the fourth ventricles, the longest diameters ranged from 3.0 cm to 4.6 cm. All these masses were totally removed via the suboccipital keyhole approach. There was no apparent neurological dysfunction postoperatively.

All the other tumors were resected totally without neurological deficits, except that in one patient with the cholesteatoma there was no alleviation of his preoperative diplopia after surgery.

4 Discussion

The Kawase's approach [4], also known as the subtemporal transpetrosal-transtentorial approach or expanded middle fossa approach, is suitable for the basilar artery aneurysm located between the sellar floor and the internal auditory canal, tumors in the upper clival region medial to the internal auditory canal, acoustic neurinomas and other tumors in the CPA. The unfolding development of the surgical facilities in the recent 20 years supplies amazing possibilities to minimize the normal expanded approaches. The subtemporal keyhole has been reported to have the same exposure field as the Kawase's approach has [1,5]. According to the lesion positions, the anterior or posterior subtemporal keyhole approach can be selected flexibly to avoid unnecessary tissue exposure.

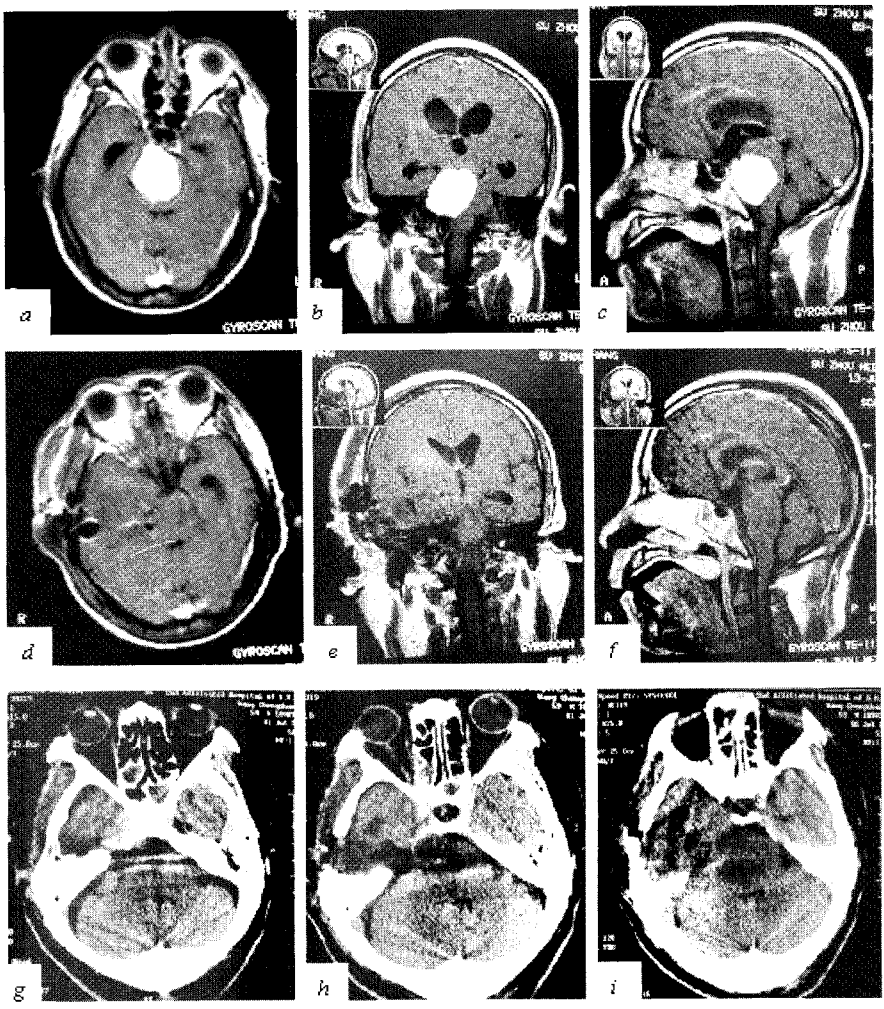


FIG. 2. The preoperative and postoperative images of one patient with a petroclival meningioma removed via a subtemporal keyhole approach. **a**, **b**, **c** Preoperative MRI; **d**, **e**, **f** MRI on the fist postoperative day; **g**, **h**, **i** CT scanning performed two weeks postoperatively, revealing the bone window and the removal range of the petrous apex

Through the subtemporal keyhole approach, the petrous apex can be removed interdurally. The removal range should also be carefully defined according to the landmarks in the skull base, in order not to damage the internal carotid artery and surrounding cranial nerves. The defect of the petrous apex can be restored with the coverage of temporal fascia and fat tissue [6] which was later fixed with glue. Moreover, we have an alternative method. When we drilled the temporal bone, we collected the bone powder. Later we used the mixture of the bone powder and the glue to revise

the bony defect. In this way, CSF leakage can be prevented effectively, without any additional resection of autogenous materials.

Our experience in this series is that through this subtemporal keyhole approach, many regions and structures can be accessed, including the petroclival region, the free margin of the tentorium, the lateral wall of the cavernous sinus, the trigeminal ganglion, the optical nerve-internal carotid artery window, the posterior internal carotid artery window, the suprasellar pituitary stalk, the dorsum sella, the supraclinoid portion of internal carotid artery, the posterior communicating artery, the oculomotor nerve, the trochlear nerve, the top of the basilar artery, the prepontine cistern, the P1 segment and the P1-P2 junction of the posterior cerebral artery, the superior cerebellar artery, the anterior and lateral aspects of the midbrain and the upper pons. Therefore this approach is proper for tumors located in the suprasellar region and the petroclival region between the internal carotid artery and the internal auditory canal. This approach is also suitable for most of the operations performed on the cavernous sinus, since it can access the lateral wall of the cavernous sinus.

Smaller incisions and craniotomies have already been applied in the normal microsurgical operations on bigger tumors in the CPA region. Furthermore, due to the advancement of retromastoid keyhole techniques, the diameter of the bone window has been reduced to approximate 2 cm, which still can meet the surgical requirements for giant tumors. If necessary, the posterior wall of the internal auditory canal can also been drilled to remove the tumor residues inside it. In this study, most of the acoustic neuromas were big and giant, yet all of which were removed 100%. For instance, the biggest one was 5.2 cm × 5.0 cm × 5.1 cm, but the function of the facial nerve in this patient was still well preserved postoperatively. However, unfortunately, in this series one patient died, because the tumor was very solid, similar to a meningioma, and tightly adherent to the brain stem. There were many feeding arteries arising from the brain stem and extending into the mass. Two days after the tumor was resected totally, the patient died from tragic respiratory arrest, due to postoperative edema occurring in the brain stem.

In the present study we find by means of the retromastoid keyhole approach some nerves like the trigeminal nerve, the facial nerve, the acoustic nerve and the lower cranial nerves, some arteries like the vertebral artery and the posterior inferior cerebellar artery, and some regions like the lateral aspect of the cerebellar hemisphere, the lateral and anteriolateral aspects of the pons can be exposed satisfactorily. Therefore this approach is no doubt suitable for the resection of tumors located in the CPA region, the petroclival region or the lateral region of the pons, like acoustic neurinomas, trigeminal neurinomas, meningiomas, etc.

In case of operations on giant tumors, the growth direction of the tumors should be well concerned. If the surgical approach is designed along the long axis of the tumor, by removing the tumor in the piecemeal fashion, the residual cavity can easily supply a proximal-to-distal manipulating space under direct vision. Therefore it is unnecessary to worry about the field of view in the direction of the long axis through the small bone window. On the other hand, whether the tumor can be totally removed mainly depends on the conditions in the direction along the transverse axis, i.e. the lateral exposure of the tumor.

As for a tumor in the fourth ventricle, thanks to the existence of the ventricle, normally it is not difficult to dissect the tumor from the inferior portion of the ventricle.

Therefore the middle suboccipital keyhole approach is suitable for the lesions in the whole fourth ventricle. Conventionally, in order to expand the exposure of the tumors in the fourth ventricle, the cerebellar vermis was incised routinely. However, our experience in this present study is that after the arachnoid membrane is opened sufficiently [7] and the cerebellum is relaxed well, the cerebellar tonsils can be retracted bilaterally, and the inferior cerebellar vermis can be easily elevated upward. Then the whole fourth ventricle region, which is superior to the foramen magnum, inferior to the aqueduct and lateral to the lateral recesses of the fourth ventricle, can be exposed completely without the sacrifice of the inferior cerebellar vermis. No doubt this approach has less iatrogenic traumatization.

Some surgeons have suggested that at the end of operations on the posterior fossa, the posterior arch of the atlas vertebra should be excised and the dura should keep open to alleviate the postoperative brain edema and to prevent the possible occurrence of cerebellar tonsillar herniation. However, with the keyhole microsurgical techniques, the reduced brain retraction usually resulted in mild brain edema. Therefore, the dura can be sutured and revised watertightly against potential CSF leakage. And it is also unnecessary to remove the posterior arch of the atlas. Under this condition, the integrity of the bony structure can be preserved.

Most of the tumors arising in the CPA region, the petroclival region, the brain stem or the fourth ventricle are located deeply inside the posterior fossa. There is a distance between the mass and the keyhole bone window. Therefore these deep big or giant tumors can be resected skillfully by use of the so-called "keyhole" effect through the small bone window. On the contrary, as to tumors in the superficial cerebellar hemisphere, bone windows have to be designed strictly according to the tumor sizes or shapes, in order to excise the tumors under direct vision.

One key step in the procedure of keyhole operations on the posterior fossa is dissecting the cisterns sufficiently for the drainage of CSF to decrease the ICP and subsequently increase the manipulating space inside the posterior fossa. But when the tumors are really so giant that the cisterns are severely influenced, intraoperative drainage of the CSF is difficult. Then a lumbar catheter preoperatively placed for intraoperative CSF drainage is of great help to the ICP reduction.

Compared with the normal microsurgical operations, the manipulating space under direct vision is diminished through the small keyhole craniotomies. Therefore the normal surgical instruments are no longer suitable, while developed tools are helpful in keyhole surgery, including an electromagnetism-controlled microscope by which the visual range and angle can be adjusted freely, and fine bayonet-shaped instruments which occupy less space and have less influence on surgical manipulation. In addition, great skills at microsurgical operations are also the necessary premises [8].

In the present series there are no complications associated with the keyhole approaches, such as tumor residues, damages to the surrounding structures, postoperative hemorrhage, etc. The general total removal rate of these tumors is up to 86.0%. These sufficiently demonstrate that microsurgical treatments of posterior cranial fossa tumors via keyhole approaches, with the safe, succinct and minimally invasive property, is one of the promising directions in modern neurosurgery.

References

1. Taniguchi M, Perneczky A (1997) Subtemporal keyhole approach to the suprasellar and petroclival region: Microanatomic considerations and clinical application. Neurosurgery 41:592–601
2. Lan Q, Huang Q, Chen J, et al (2001) Clinical application of the supraorbital keyhole approach assisted by neuroendoscope. Jiangsu Med J 27:357–360
3. Lan Q, Zhang QB, Shen LM, et al (2002) Microsurgical treatments of intracranial aneurysms via keyhole approaches. China J Neurosurg Dis Res 1:304–307
4. Kawase T, Toya S, Shiobara R, et al (1985) Transpetrosal approach for aneurysms of the lower basilar artery. J Neurosurg 63:857–861
5. Kocaogullar Y, Avci E, Fossett D, et al (2003) The extradural subtemporal keyhole approach to the sphenocavernous region: Anatomic considerations. Minim Invasive Neurosurg 46:100–105
6. Yoshida K, Kawase T (1999) Trigeminal neurinomas extending into multiple fossae: Surgical methods and review of the literature. J Neurosurg 91:202–211
7. Yan PX, Wang ZC, Yu CJ, et al (2004) Microsurgical treatment of cranial-cervical type giant ependymoma within the fourth ventricle in adult patients. Natl Med J China 84:628–631
8. Zhao JZ (2004) Present status and unresolved problems in the field of minimally invasive neurosurgery. Natl Med J China 84:793–795

The NASA Nanoelectrode Array for Deep Brain Stimulation: Monitoring Neurotransmitters and Electrical Activity Plus Precise Stimulation

Russell Andrews[1], Jun Li[1], Alan Cassell[1], Jessica Koehne[1], Meyya Meyyappan[1], Barbara Nguyen-Vu[1], Neng Huang[2], and Li Chen[2]

Summary. Deep brain stimulation (DBS), often referred to as neuromodulation, is a recently-established treatment for advanced Parkinson's disease. However, current techniques utilize large macroelectrodes (>1 mm diameter) under open-loop conditions (i.e. no internal feedback to guide the stimulation). The use of multi-walled carbon nanotubule nanoelectrode arrays can both improve the resolution of brain electrical activity monitoring, and add monitoring of neurotransmitters (e.g. dopamine)—in addition to precise focal electrical stimulation under closed-loop conditions. An overview of the characteristics and potential of nanoelectrode arrays for DBS/neuromodulation is presented.

Key words. deep brain stimulation, carbon nanotubule, nanoelectrode, neuromodulation, Parkinson's disease

1 Introduction

Deep brain stimulation (DBS, neuromodulation) has been developed over the last 15 years as an effective treatment for movement disorders such as Parkinson's disease and essential tremor. DBS will likely prove effective for epilepsy, depression and other mood disorders, and eating disorders as well [1]. Current techniques for DBS utilize macroelectrodes (>1 mm diameter) which provide imprecise stimulation. In addition, the stimulation is open-loop (i.e. the stimulation is not guided by monitoring of brain electrical or neurochemical activity), which is not only wasteful (the stimulation is constant) but is also of suboptimal effectiveness. Marked improvement in DBS could be realized by combining continuous monitoring of neurotransmitter levels and electrical activity with precise electrical stimulation (electrochemical closed-loop neuromodulation). Most importantly, reducing the scale to the nano level (1) improves signal-to-noise ratios, (2) permits greater precision (down to the subnuclei level) and

[1] NASA Ames Nanotechnology, Moffett Field, 244 Mistletoe Road, Los Gatos, CA 95032, USA,
[2] The Parkinson's Institute, Sunnyvale, CA, USA

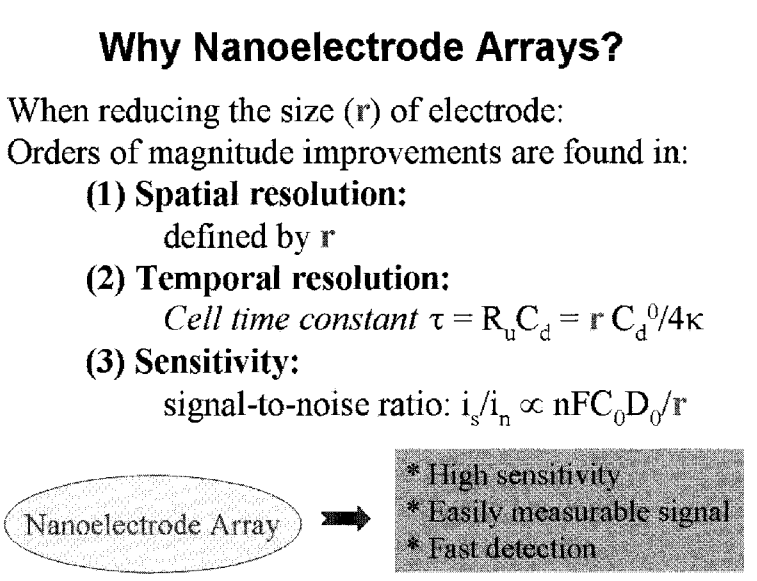


FIG. 1. Improved (1) spatial resolution, (2) temporal resolution, and (3) sensitivity with nanoelectrode arrays

(3) allows multiple recording/monitoring and stimulation sites throughout the central nervous system (Fig 1) [2].

2 Materials and Methods

The NASA Ames Nanotechnology Center is developing microchip nanoelectrode arrays for neuromodulation that permit monitoring of electrical activity and neurotransmitter levels plus precise electrical stimulation in a closed-loop (feedback) manner [3–5]. The microchip consists of two types of vertically-aligned multi-walled carbon nanotube (CNT) arrays on multiple individually addressed microelectrode pads (Fig 2). The first type, the stimulation electrode, is a forest-like carbon nanotube array which presents a large surface area, ideal for stimulation. The second type is insulated, leaving only the very end of the carbon nanotube arrays exposed at the surface to form an inlaid nanodisk electrode array.

Carbon nanofibers (CNFs) can be grown vertically as prepatterned electrodes on a silicon wafer by a plasma enhanced chemical vapor deposition (PECVD) process [5]. Coating the CNFs with an electroactive polymer film (e.g. polypyrrole) not only stabilizes the CNFs but also improves biocompatibility and decreases electrical impedance (important for effective tissue stimulation). The insulation is a silicon oxide, followed by chemical-mechanical polishing to leave only the tips of the CNFs exposed (Fig 3).

We have recently studied the growth of the PC12 cell line on the nanoelectrode arrays. PC12 is a neuron-like cell line derived from a transplantable rat pheochromocytoma which can produce catecholamines upon selective stimulation. For example,

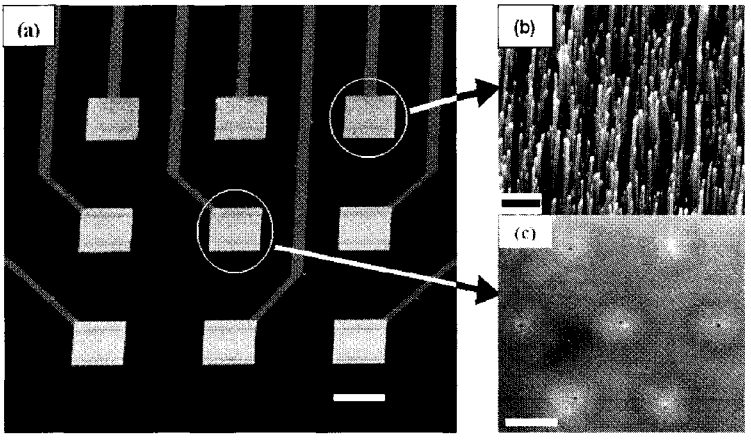


FIG. 2. SEM image of (1) a 3 × 3 microelectrode array, (2) exposed CNT array for electrical stimulation, (3) embedded low-density CNT array for recording electrical activity and changes in local neurotransmitter concentrations. *Scalebars* are 200 μm, 1 μm, and 2 μm respectively

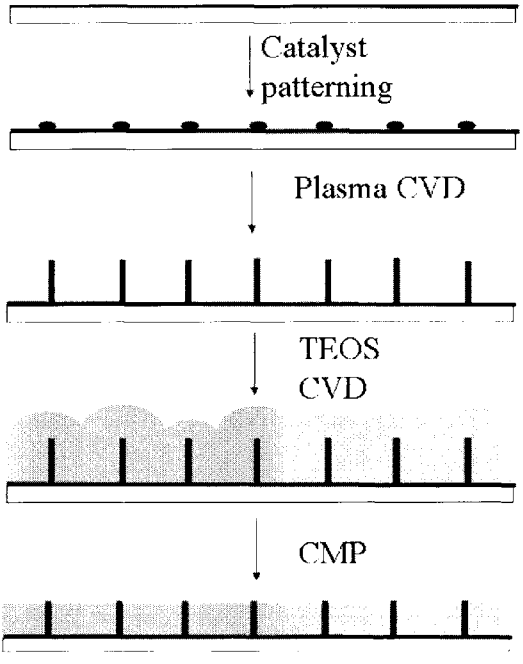


FIG. 3. Fabrication schematic of CNT electrode array. *CVD*, chemical vapor deposition; *TEOS*, tetraethylorthosilicate; *CMP*, chemical-mechanical polishing

high concentration K^+ preferentially induces the release of dopamine. The dopamine release in response to high concentration K^+ averages 11 pmol $min^{-1} \times 10^6$ $cells^{-1}$ above control, making the PC12 an ideal in vitro model cell line for evaluating the CNF nanoelectrode array as novel DBS electrode for use in Parkinson's disease, since dopamine deficiency in the basal ganglia is the principal abnormality in Parkinson's disease.

3 Results

The insulated nanoelectrode array has very remarkable electrochemical properties, with a detection limit of redox species down to a few nanomolars plus an extremely high temporal resolution (milliseconds). These properties are ideal for measuring simultaneously (1) extracellular neurotransmitters (e.g. dopamine, glutamate) and (2) focal electrical activity. The uninsulated array is excellent for electrical stimulation, for example as a focal (or regional) closed-loop stimulation system where precise stimulation is directed by changes in the monitored electrical activity and/or neurotransmitter concentration. Future plans include implanting the array in small animal models for Parkinson's disease.

4 Conclusions

It is likely that some form of nanoelectrode array such as that presented above will present a major improvement in DBS/neuromodulation. Electrochemically-guided closed-loop multisite DBS/neuromodulation with nanoelectrode arrays will afford the possibility of much more precise therapy for many nervous system disorders beyond the current application in movement disorders such as Parkinson's disease. Examples of these potential applications include intractable epilepsy, as well as disorders of mood and eating.

References

1. Andrews RJ (2003) Neuroprotection trek—next generation: Neuromodulation I. Techniques—deep brain stimulation, vagus nerve stimulation, and transcranial magnetic stimulation. Ann N Y Acad Sci 993:1–13
2. Li J, Ng HT (2003) Carbon nanotube sensors. In: Nalwa H (ed.) Encyclopedia of Nanoscience and Nanotechnology. America Scientific Publishers, CA, USA
3. Koehne J, Li J, Cassell AM, et al (2004) The fabrication and electrochemical characterization of carbon nanotube nanoelectrode arrays. J Mater Chem 14:1239–1245
4. Li J, Cassell A, Delzeit L, et al (2002) Novel three dimensional electrodes: electrochemical properties of carbon nanotube ensembles. J Phys Chem B 106:9299–9305
5. Li J, Ye Q, Cassell A, et al (2003) Bottom-up approach for carbon nanotube interconnects. Appl Phys Lett 82:2491–2493

Part 2
3rd World Congress of the Academy for Multidisciplinary Neurotraumatology

Phenomenological Aspects of Consciousness: Coma Scale in Chronic Stage (Chronic Coma Scale Score; CCSs)

Tomio Ohta

At the last two congresses of AMN, phenomenological aspects of consciousness disturbance in acute stage were revisited, and proposed a new coma scale—Emergency Coma Scale (ECS), which consisted of the combination of Glasgow Coma Scale and Japan Coma Scale[1]. And further, conceptual differences between consciousness and mind were discussed from the viewpoint of the care of demented patients.

This time, we are going to present a new coma scale in chronic stage. In this chronic coma scale score (CCSs), each components of contents of consciousness including level of arousability are included, and mental function is out of analysis because of the secondary subject in coma scales. Mental dysfunction should be either aggravated or improved parallel to the conscious disturbance.

The most basic works in CCSs are to assess the several components of conscious contents, such as intelligence, emotion, volition, and arouzability either by means of question or observation. Also assessments of the conscious disturbance in the chronic stage should be considered into the 3 stages, in which the patients are institutionalized, visit out-patient clinic, and are reinstated. Finally, CCSs would be applied to use in either ways of improvement or aggravation in the processes of aging in such a rapid aging society.

Reference

1. Ohta T (2005) Phenomenological aspects of consciousness—its disturbance in acute and chronic stages. Acta Neurochir (Wien) [Suppl] 93:165–167

Institute of Brain Function, Iseikai Hospital, Osaka, Japan

Right Median Nerve Electrical Stimulation for the Vegetative State

EDWIN COOPER[1], BRYAN COOPER[2], and JEFFERSON CHEN[3]

Summary. The right median nerve is a portal to electrically stimulate and help arouse the central nervous system for persons with reduced levels of consciousness. The mechanisms of central action include increased cerebral blood flow and raised levels of norepinephrine and dopamine. The experience in the United States with nerve stimulation for acute coma after traumatic brain injury is over ten years in duration. There is a longer period of experience by neurosurgeons in Japan with implanting electrodes on the cervical spinal cord of persons in the persistent vegetative state. The use of right median nerve electrical stimulation (RMNS) for patients in the chronic phases of unconsciousness is relatively new. A young woman in Oregon (U.S.A.) was in a vegetative state ten months after multiple injuries including a severe brain injury from which survival was not expected. A video documents her progress of walking and talking after one year of RMNS. Regardless of the etiology of the coma or reduced level of awareness, electrical stimulation may serve as a catalyst to enhance central nervous system functions. It remains for the standard treatments and modalities to retrain the injured brain emerging from reduced levels of consciousness.

Key words. median nerve, electrical stimulation, vegetative state

Traumatic brain injury (TBI) is caused by motor vehicle crashes, falls, violence and sports injuries. TBI is twice as frequent in males than in females with 52,000 annual deaths in the United States [1]. The highest incidence is among persons 15 to 24 years of age but there are peak in the very young and the elderly. TBI may result in life long impairment of physical cognitive psychosocial functions. Prevalence of those with the chronic disability is between 2.5 and 6.5 million persons. About two million persons each year have a TBI. Up to 90,000 incur a TBI resulting in life long impairments.

[1] Department of Neurosurgery, University of Virginia Health System, Charlottesville, VA, 1001 North Queen Street, Kinston, NC 28501, U.S.A., [2] East Carolina Neurology, Brody School of Medicine, East Carolina University, Greenville, NC, U.S.A., and [3] Director of Neurotrauma, Legacy Emanuel Hospital, Portland, OR, U.S.A.

Three decades ago, at the University of Virginia (UVa), electrical stimulation was used for a specific set of neuromuscular deficits. In 1972, radio-linked electrodes were implanted on the sciatic and femoral nerves of a paraplegic teenage boy to attempt ambulation [2]. In the mid and late 1980's, functional electrical stimulation was done on the surfaces of quadriplegic persons' forearms at East Carolina University (ECU) School of Medicine, North Carolina State University, Department of Industrial Engineering, and then at the Department of Biomedical Engineering at Duke University. The latter two projects employed a voice controlled hardware/software program for the quadriplegic subject to give commands to his/her paralyzed hand [3]. Next the same equipment was used for electrical enhancement of motor learning in persons with mental/motor developmental delays at Caswell Center in Kinston, North Carolina. In the early 1990's there was an electrical stimulation project for teenage head injury patients at the A.I. DuPont Institute in Wilmington, Delaware. In the early 1990's through the present, there have been parallel pilot studies at the medical center of East Carolina University in Greenville, North Carolina and also the Department of Neurosurgery at the University of Virginia in Charlottesville, Virginia [4–6]. The focus of the coma studies at ECU and UVa has been toward young people with traumatic brain injury from motor vehicle crashes resulting in coma with Glasgow Coma Scales (GCS) less than 8.

Transcutaneous electrical stimulation has been applied to the median nerves of the subjects, usually starting within the first two weeks post injury while still in coma. This has resulted in quicker awakening than a control group which would receive sham stimulation [4,6].

The right median nerve was selected as the portal for the application of the electrical pulses (300 microsecond duration, 40 pulses per second, 20 s and 40 s off for 8 h a day). The Focus electrical neuromuscular stimulator (EMPI, St. Paul, MN, U.S.A.) has been used for the median nerve stimulation for several years. The right median nerve was preferred because of the dominance of the left hemisphere in most subjects whether left or right handed.

The electrical stimulation delivered over the median nerve enters as electrochemical impulses into the brain through multiple peripheral pathways and accesses a similar multiplicity of central pathways. The cortical representation of the hand is proportionately the largest of all extremities. It is significantly larger than in primates and remarkably larger than that in other lower animals. Electrical stimulation transcutaneously entering into the median nerve passes up through both the spinothalamic and the spinoreticular pathway of the anterolateral system. There are synaptic connections in the spinoreticular and ascending reticular activating system (ARAS) distributed through the mid pons and lower midbrain [7]. These spinoreticular synapses cause excitation of the locus coeruleus, the center producing norepinephrine in the brainstem, and has direct cortical connections. There is a diffuse input of norepinephrine to cortical layers 1 and 2 from the ARAS. Stimulation of these pathways causes a diffuse arousal process. The ARAS also has direct connections to the basal nucleus of Meynert. This nucleus is well known to be one of the major acetylcholinergic producers within the brain. Stimulation from the ARAS to the basal nucleus of Meynert causes a diffuse acetylcholinergic input to all lobes of the cortex. This causes some amount of arousal, but is also a mechanism for maintenance of long-term potentiated circuitry, most importantly the ability to speak. A separate connec-

tion in the anterolateral system is the spinothalamic component which has synaptic inputs directly to the intralaminar nuclei of the thalamus. These nuclei are well known to be causative in the startle response which may cause a brief hyperawareness. Separate connections within the spinothalamic pathway go directly to the ventral posterolateral (VPL) nucleus of the thalamus. The VPL is responsible for interpreting sensory information from the contralateral hemi-body [7]. The stimulation to this nucleus is then processed on through third order neurons that terminate in the primary somato-sensory strip. These stimuli have been shown in blood flow sensitive sequences of functional MRI with concomitant median nerve electrical stimulation [8]. Then through multiple connections, impulses are transmitted to Broca's expressive speech center through arcuate fibers. This stimulation of surviving language pathways after TBI is a mechanism of maintaining the quicker return of speech upon awakening of the comatose individual. This has been observed anecdotally and through basic research [6].

In recent years, the same methodology has been used for persons at the subacute coma stage and also those in the vegetative state, over three months post injury.

Experience in Japan goes back to the mid 1980's. The neurosurgeons have implanted electrodes on the posterior column of the cervical spinal cord trying to hasten awakening of patients in long-term vegetative states [9,10]. The neurophysiological mechanisms found by testing the spinal fluid, neuroimaging studies, and electroencephalograms, have all demonstrated the central nervous system effect of dorsal column electrical stimulation (DCS). RMNS has been used in more recent years in Japan and the U.S.A. for the long-term patients. It is anticipated that the targets in the thalamus are the same for both methods, DCS or RMNS.

Cerebral blood flow and dopamine are increased by electrical stimulation [9–11]. These neurocirculatory changes induced by stimulation accelerate awakening from coma or the vegetative state.

Consistent factors affecting outcome after electrically treated traumatic brain injury have been noted in Japan and the U.S.A. The severity and nature of the brain injury are the most important factors. Those patients with severe structural damage of the brain fair worse. Anoxic brain injury is harder to treat electrically than traumatic brain injury. The age of the patient had some influence, the best results occurring in the adolescent years. But there have been a few elderly patients who have responded to electrical stimulation well. A very important factor is the time between the injury and the onset of the electrical stimulation. Generally, the sooner the stimulation is started the better the outcome [12].

A series of twelve Glasgow Coma Scale of 4 coma patients treated with early right median nerve stimulation at East Carolina University Medical Center (teenagers and young adults) showed good recovery in 4 out of 12 cases (33%) and moderate disability in 3 out of 12 cases (25%). Therefore, over half of these severely injured patients who survived their injury, made a satisfactory recovery when the electrical stimulation was begun in the first few weeks post injury [13].

Experience using electrical stimulation applied to the right wrist is much smaller in patients who are already months or years post brain injury. One outstanding example is KM, in Portland, Oregon. KM was in a motor vehicle crash in December 1999 at age 20.

KM had severe diffuse brain injury with multiple cerebral contusions and subarachnoid hemorrhage, multiple fractures (neck, clavicle, pelvis), right renal laceration, and possible hypoxic encephalopathy. A right frontal ventriculostomy was done but her intractranial pressures rose to 40 mmHg overnight. On December 26th she had an emergency left frontotemproparietal decompressive craniectomy with evacuation of a subdural hematoma. Posterior cervical fusion of C1–2 was done because of a fracture. Later the skull bone flap was replaced in February of 2000.

Initially in a coma, KM went into a vegetative state which persisted. She was in PVS when electrical stimulation was considered ten months post injury. A ventriculoperitoneal shunt was done for hydrocephalus. Median nerve stimulation was started in October of 2000. Within a few days, KM became more interactive with her mother. The surface median nerve stimulation was first on the right wrist for 8 h a day, and later the stimulation was alternated between both median nerves. She walked with the help of two persons within a year. After two years of bilateral alternating median nerve electrical stimulation and acupuncture, neurological recovery continued. She mouthed words for the first time three years post injury (two years after the start of the electrical treatment). Now five years post injury, KM can walk with the help of one person. She whispers phrases out loud and is able to feed herself. Her facial expressions are more interactive and prompt when her mother talks to her in 2005 compared to previous years.

Conclusion

With his wealth of experience in neurotrauma, Professor John Jane, Chairman of Neurological Surgery at the University of Virginia, stated: "Very few things do work in this situation and if your techniques make any difference whatsoever, I think it would be well worth it" (J Jane, 1995, personal communication).

Electrical stimulation may serve as a catalyst to enhance central nervous system recovery in awakening from coma and improvement in function, especially speech. The electrical stimulation serves mainly to "switch on" the central nervous system. It remains for standard treatments (physical therapy, occupational therapy, speech therapy, neurocognitive education, and medications) to retrain the injured brain emerging from reduced level of consciousness. The comatose brain is alive. We can interact with it through electrical stimulation. RMNS can shorten the time in coma and may improve the final functional outcome.

References

1. Gordner R, Tuel S (1998) Rehabilitation of persons with traumatic brain injury. NIH Consens Statement 16:1–29
2. Cooper E, Bunch W, Campa J (1973) Effects of chronic human neuromuscular stimulation. Surg Forum 24:477–479
3. Cooper E, Han D, McElhaney J, et al (1988) A voice controlled computer system for restoring limited hand functions in quadriplegics. Proceedings AVIOS voice input/output systems applications conference. San Francisco, CA
4. Cooper J, Jane J, Alves W, et al (1999) Right median nerve electrical stimulation to hasten awakening from coma. Brain Inj 13:261–267

5. Peri C, Shaffrey M, Farace E, et al (2001) Pilot study of electrical stimulation on median nerve in comatose severe brain injured patients: 3-month outcome. Brain Inj 15:903–910
6. Cooper E, Cooper J (2003) Electrical treatment of coma via the median nerve. Acta Neurosurgica [Suppl] 87:7–10
7. Parent A (1996) Carpenter's human neuroanatomy. Williams & Wilkins, Baltimore, MD, pp 381–383, 633–654
8. Spiegel J, Tintera J, Gawehn J, et al (1999) Functional MRI of human. Clin Neurophysiol 110:47–52
9. Kanno T, Kamei Y, Yokoyama T (1992) Treating the vegetative state with dorsal column stimulation. Soc Treat Coma 1:67–75
10. Yokoyama T, Kamei T, Kanno T (1996) Right median nerve stimulation for comatose patients. Soc Treat Coma 5:117–125
11. Liu J, Wang C, Chou I, et al (2003) Regaining consciousness for prolonged comatose patients with right median nerve stimulation. Acta Neurosurgica [Suppl] 87:11–14
12. Cooper E, Cooper J (2003) Electrical treatment of comatose teenagers via the median nerve. Acta Neurosurgica 145:1140–1141
13. Cooper E, Kanno T (2005) Electrical treatment of coma. In: Carrion J, von Wild K, Zitnay G (eds) Brain injury treatment: theories and practices. Psychology Press, New York

An Ecologically Valid System for Classifying Severity of Traumatic Brain Injury in Children

George P. Prigatano

Summary. The classification of severity of traumatic brain injury in children remains difficult, especially for those considered to have "mild" and/or "moderate" brain injury. In an ongoing study at the Barrow Neurological Institute, we classified 85 children using a method that appears to have ecological validity. Children are classified as mild uncomplicated, mild complicated, moderate secondary to focal brain injury, moderately severe, and severe. One to two years postinjury, groups differ on speed of information processing, the percent that requires special education, and independent parental ratings regarding their child's recovery level and return to normal social integration.

Key words. traumatic brain injury, children, severity, outcome

1 Introduction

The Glasgow Coma Scale (GCS) has been extremely helpful in classifying severity of traumatic brain injury (TBI) in adults [1]. While it also has been applied to children, investigators have noted its limitations, particularly when classifying "mild" to "moderate" brain injuries [2–4]. Levin et al [4] also noted that the systematic assessment of the period of post-traumatic amnesia following pediatric TBI was more strongly related to postacute memory impairment than GCS scores per se.

Fletcher et al [3] further noted that (1) GCS scores obtained in the emergency rooms (ER) may be higher than scores obtained 24 h later because some children deteriorate. (2) Children with GCS scores between 9 and 12 (in the so-called moderate range) may actually have severe brain injuries if the motor scale score on the GCS is below 6 in 24 h. (p. 10) Bruce [5] highlighted other complexities in classifying severity of TBI

Division of Neurology, Barrow Neurological Institute, St. Joseph's Hospital and Medical Center, 350 West Thomas Rd., Phoenix, AZ 85013, U.S.A.

in children and noted, among other variables, that the presence of multiple trauma resulted in a worse outcome for any given level of GCS scores.

While acute neuroimaging studies of children may underestimate the degree of brain pathology [5], the presence of a space-occupying lesion often suggests a more severe injury than what the GCS score in and of itself suggests. For example, Brookshire et al [6] recently noted that if a child had a GCS score of 13 to 15 (typically considered a mild TBI) but had evidence of a brain lesion on computed tomography (CT) or magnetic resonance imaging (MRI) within 3 months of injury, the child was considered to have sustained a moderate TBI.

Since severity of TBI has been shown to relate to long-term neuropsychological outcome in adults [7], clinicians need a simplified method of classifying severity of TBI in children that has ecological validity (i.e., relates to real world performance within 1 to 2 years of injury). Clinically, it would appear that children who have suffered an intraparenchymal brain lesion, as evidenced by CT or MRI findings, have suffered a "worse" injury than a child who may show lesions, which are extraparenchymal (e.g., presence of a subdural hematoma or skull fracture).

In the course of an ongoing study on parents' perceptions of children's recovery after TBI, a system for classifying severity of TBI was developed. The classification system reflected the "natural" distribution of findings documented in medical records. In this retrospective chart review, children were classified on the basis of their GCS scores when first admitted to the ER and on the presence of abnormal findings on neuroimaging. The children were classified according to the following system:

Severe TBI: Admitting GCS between 3 to 8 (if no GCS available, unequivocal evidence of loss of consciousness (LOC) for at least 24 h.

Moderate severe TBI: Admitting GCS between 9 to 12 with a clear space-occupying lesion or associated skull fracture.

Moderate injury secondary to focal damage: Children may have no LOC or brief LOC, but clear findings of cerebral contusion on CT. Typically, these children are not involved in motor vehicle accidents but suffered falls or blows to the head.

Mild complicated TBI: Admitting GCS between 13 to 15, with or without initial evidence of LOC. On neuroimaging all children have skull fractures, subdural hematomas, or epidural hematomas. There was no lesion within the brain per se.

Mild uncomplicated TBI: Admitting GCS between 13 to 15 with positive LOC or, at minimum, "confusion" at time of injury. No positive findings on CT or skull x-ray.

If this classification is helpful, one should observe two basic findings: (1) a stepwise increase in objective neuropsychological impairments in children who have progressively more severe TBI and (2) a stepwise increment in parental judgments concerning overall recovery of their children.

A major issue in understanding the neuropsychological and psychosocial consequences of children with mild TBI (complicated or uncomplicated) is having an appropriate comparison group. The behavior of these children may put them at risk for such injuries. One must therefore study trauma controls in relationship to these five levels of severity. A trauma control is defined as a child who has suffered significant enough orthopedic injury to also be admitted to the ER of a hospital.

The present investigation studied children using neuropsychological test findings and parents' reports as a function of severity of brain injury. The primary question asked was as follows: Does this system of classifying severity of TBI have ecological

validity? That is, does it correlate with performance on neuropsychological tests and parents' judgments of a child's functioning in a stepwise fashion?

2 Methods

2.1 Subjects

Eighty-five children enrolled in an ongoing study on parental perspectives regarding recovery after TBI in childhood served as subjects. Inclusionary criteria were as follows:

(1) Age at time of entry into the study between ages 7 and 14.
(2) Parental consent to examine the child with neuropsychological tests and parental agreement to complete questionnaires regarding their child's history and present functioning.
(3) History of unequivocal TBI as documented in the ER records, with clear documentation as to severity of injury. For trauma controls, there needed to be clear documentation of orthopedic injuries with no evidence of acquired TBI.
(4) Primary language was English or the child spoke English at a comparable level to Spanish.

Exclusionary criteria were as follows:

(1) Parents' report of preexisting psychiatric, neurological, or learning difficulties (i.e., history of learning disability).
(2) NonEnglish speaking parents.
(3) Mechanism of injury was secondary to gunshot wound, abuse, or a suicide attempt.
(4) Death of family member at the time of accident or injury.
(5) Residing outside Maricopa County and could not drive the distance to be examined.

2.2 Procedures

All subjects were enrolled in the study after ER records from St. Joseph's Hospital and Medical Center were retrospectively reviewed. Once potential subjects were identified, phone calls were made to the child's parents to explain the purpose of the study and to solicit parents' involvement in the study. If parents agreed to participate but failed to keep their appointment, a second call was made. If the patient's family did not return the call, no further contact was made. In the event that the patient's family failed to keep two appointments, no further contact was made.

Four-hundred fifty children with identifiable history of TBI and 301 patients with orthopedic injuries were initially identified. Two thousand, one-hundred and eighty-three phone calls were made. As noted above, 85 children were eventually enrolled in the study. Primary reasons for failure to enroll the child in the study were as follows: subjects were excluded based on exclusionary criteria; the parent was unwilling or unable to participate in the study; inability to contact families by phone (i.e., wrong numbers or disconnected phone number), or failure to keep two appointments.

2.3 Materials and Testing Protocol

Prior to testing the patient and to obtaining questionnaire information from the parents, informed consent was obtained from the parents and for children 12 years of age or older.

Children were then examined by either a board-certified clinical neuropsychologist, a resident in clinical neuropsychology, or a graduate student trained to administer neuropsychological tests. The children were administered the Vocabulary, Block Design, and Digit Symbol subtests of the Wechsler Intelligence Scale for Children-Third Edition [8], the BNI Screen for Higher Cerebral Functions for School-Age Children [9], the Halstead Finger Tapping Test [10], and a BNI Adaptation of the Fuld Object Memory Test [11].

Parents completed three questionnaires. One questionnaire was designed specifically for this study and was entitled: "The Care of Children with Traumatic Brain Injury in Maricopa County." Several questions were asked concerning their view of the child's recovery, social integration, and distress level that they experienced in managing the child. In addition, the parents completed the Child Behavioral Checklist [12] and the Children's Family Behavioral Information Sheet used in the Section of Clinical Neuropsychology, Barrow Neurological Institute (unpublished). This latter questionnaire obtained demographic information concerning the child as well as the family.

Time to complete the neuropsychological testing was approximately 45 to 60 min. Time for the parent to complete the three questionnaires was about 60 min.

All children and family members were told that participation in the study was voluntary and that they could discontinue their participation at any time. All understood this instruction and all agreed to continue the testing and completion of the forms once they began.

For purposes of this study, only the findings obtained on the Wechsler Intelligence Scale for Children-Third Edition will be presented as well as three ratings obtained from the "Care of Children with Traumatic Brain Injury in Maricopa County" questionnaire. On that questionnaire, parents were asked if their child was receiving special education services at the time of the examination. They were also asked to rate on a five-point scale their child's level of recovery as well as their re-integration into social life (0 = no recovery, 1 = poor recovery, 2 = fair recovery, 3 = good recovery, 4 = excellent recovery, 5 = complete recovery).

Parents were also asked whether the child received special education services prior to their injury. While children were to be excluded if they had a preexisting learning disability, we discovered after enrollment that a few children, in fact, did have a preexisting learning disability. This issue is discussed in more detail below.

2.4 Statistical Analyses

Descriptive statistics were obtained concerning demographic information and performance on various neuropsychological tests. One-way analyses of variances (ANOVA) were conducted to determine if a main effect was obtained on neuropsychological tests, family reports concerning the childs' recovery level, and social integration. Percentage of children receiving special education services was calculated. If

TABLE 1. Summary of demographics

Group	*n*	Mean age when tested	% Male	Chronicity in years
Trauma controls	17	9.88	58.8	1.05
TBI mild uncomplicated	19	10.32	68.4	0.99
TBI mild complicated	20	11.35	65.0	1.07
Moderate secondary to focal injury	8	11.88	87.5	1.03
Moderate severe to severe TBI combined	21	11.10	61.9	2.23
Total	85	10.81	65.9	1.33
		$F = 1.415$		$F = 2.127$
		$P = 0.236$		$P = 0.085$

an overall main effect was obtained, specific group comparisons were made to determine if there were differences at the 0.01 level.

2.5 Classification of Brain Dysfunction

The classification system used is described in the *Introduction.*

3 Results

Table 1 summarizes the demographic information of the various children studied. Trauma controls were on the average 9.88 years while children with TBI tended to be between 10.5 and 11 years of age. The mean difference was not statistically reliable. However, it should be noted that trauma controls were a year younger and this could affect some of the findings obtained.

Approximately two-thirds of all TBI children were boys, which is comparable to the known demographics of these children [13]. Children with mild TBI were approximately 1 year post-trauma. Children with moderate severe to severe TBI were approximately 2 years post-trauma. The differences, however, did not reach statistical significance ($F = 2.27$, d.f. $= 4$, $P = 0.085$).

Tables 2 and 3 list the frequency (and percentage) of children receiving special educational services before and after TBI. As Table 2 illustrates, there is a clear stepwise increment in the percentage of children receiving special education services as a function of severity of TBI. While the initial screening of children specifically was to exclude children with learning disabilities, we discovered that a few children were, in fact, enrolled in the study. Table 3 presents the percentage figures obtained for preexisting learning disabilities in each of the classification groups. As can be seen, there was a clear increment in the percent of children receiving special education services after moderate and after moderate severe to severe TBI. Children with moderate injury secondary to focal damage doubled the percentage receiving special education services. For children with moderate severe to severe TBI, the figure tripled.

Neuropsychological test performance also showed a clear stepwise increase as a function of more severe injuries. The Coding Subtest scores clearly illustrated this finding (see Table 4). An average score is 10 with a standard deviation of 3. Trauma controls as well as children with mild uncomplicated TBI showed a normal perfor-

TABLE 2. Parental perspectives: Is your childreceiving special education services?

	n	Yes (%)
Trauma controls	16	0.0
TBI mild uncomplicated	19	5.3
TBI mild complicated	19	15.8
Moderate secondary to focal injury	8	25.0
Moderate severe to severe TBI combined	19	36.8
Total	81	16.0

TABLE 3. Parental perspectives: Did your child receive special education services prior to their medical problem? (i.e., TBI or trauma controls)

	n	Yes %
Trauma controls	16	0.0
TBI mild uncomplicated	18	5.6
TBI mild complicated	17	11.8
Moderate secondary to focal injury	8	12.5
Moderate severe to severe TBI combined	21	9.5
Total	80	7.5

TABLE 4. Neuropsychological test findings: WISC-III age-adjusted scaled scores (mean values)

	n	Vocabulary	Block design	Coding
Trauma controls	16	10.00	11.44	11.19
TBI mild uncomplicated	19	11.11	11.63	11.00
TBI mild complicated	20	11.45	11.20	9.10
Moderate secondary to focal injury	8	9.88	10.13	10.50
Moderate severe to severe TBI combined	21	8.33	8.76	6.71
		F = 2.431	F = 2.047	F = 7.397
		$P = 0.054$	$P = 0.096$	$P = 0.000$

mance on this test. However, children with moderate severe to severe TBI showed clearly impaired performance. It is interesting to note that children with moderate injuries secondary to focal damage (assume not to have diffuse axonal injury) performed at a level comparable to trauma controls and mild uncomplicated TBIs. Children with moderate severe to severe TBI significantly differed (at least the 0.01 level) from trauma controls, children with mild uncomplicated TBI, and those with moderate injuries secondary to focal damage ($P = 0.01$; see Table 4).

Parental ratings of the child's overall recovery were also clearly related to severity of TBI (F = 9.244, d.f. = 4, $P = 0.001$). As Table 5 illustrates, children with moderate severe to severe TBI were rated as having less recovery than trauma controls, children with mild uncomplicated and mild complicated TBI, but they were not different from children with moderate injury secondary to focal damage. The same pattern was observed when asking parents to rate their child's level of social reintegration 1 to 2

TABLE 5. Parental perspectives: Rate your child's overall level of recovery

	n	Mean	SD
Trauma controls	16	4.63	0.50
TBI mild uncomplicated	18	4.28	0.67
TBI mild complicated	19	4.21	0.85
Moderate secondary to focal injury	8	3.88	0.99
Moderate severe to severe TBI combined	21	3.24	0.77
Total	82		
		F = 9.244	
		P = 0.000	

0, no recovery; 1, poor; 2, fair; 3, good; 4, excellent; 5, complete.

TABLE 6. Parental perspectives: Rate your child's integration back into social life (including school, home, with friends, etc.)

	n	Mean	SD
Trauma controls	16	4.75	0.47
TBI mild uncomplicated	19	4.32	0.92
TBI mild complicated	19	4.37	0.97
Moderate secondary to focal injury	8	3.75	1.55
Moderate severe to severe TBI combined	21	3.19	0.93
Total	83		
		F = 8.284	
		P = 0.000	

0, no recovery; 1, poor; 2, fair; 3, good; 4, excellent; 5, complete.

years post-trauma. Again, a significant overall effect was obtained (F = 8.284, d.f. = 4, $P = 0.001$; Table 6). The same stepwise relationships were observed.

4 Discussion

Having an ecologically valid system for documenting severity of TBI in children is important for understanding a wide variety of cognitive, behavioral, and educational difficulties that these children present with 1 to 2 years post-trauma. In this preliminary report, children with moderately severe to severe TBI had a higher incidence of receiving special education services after injury, performed more poorly on neuropsychological tests (particularly a test of speed of information processing), and were judged to have less overall recovery and social integration after their injury. Also, as the level of severity of injury increased, the percentage of children receiving special education also increased. As the level of injury increased, a stepwise increment in level of neuropsychological impairment was noted and in parents' judgments of the child's level of recovery and social integration.

It would require a very large sample to determine whether significant differences exist between the various subgroups classified in this study. However, the initial findings are encouraging and suggest that careful delineation of features that would

describe mild complicated versus uncomplicated injuries and injuries that are moderate secondary to focal damage may help us better understand the various outcomes observed in TBI children.

5 Conclusions

Children who suffer TBI often show varied and unpredictable outcomes when their initial GCS scores are considered. Combining GCS scores with neuroimaging findings suggests that one can establish a more "ecologically valid" system for classifying severity of brain injury. The present findings suggest that the classification system employed relates to parental perceptions of the child's recovery and to the child's performance on neuropsychological tests 1 to 2 years post-trauma.

References

1. Teasdale G, Jennett B (1974) Assessment of coma and impaired consciousness. A practical scale. Lancet 2:81–84
2. Asarnow RF, Satz P, Light KZ, et al (1995) The UCLA study of mild closed head injury in children and adolescents. In: Broman SH, Michel ME (eds) Traumatic head injury in children. Oxford University Press, New York, 117–146
3. Fletcher JM, Ewing-Cobbs L, Francis DJ, et al (1995) Variability in outcomes after traumatic brain injury in children: A developmental perspective. In: Broman SH, Michel ME (eds) Traumatic head injury in children. Oxford University Press, New York, pp 3–26
4. Levin HS, Ewing-Cobbs L, Eisenberg HM (1995) Neurobehavioral outcome of pediatric closed head injury. In: Broman SH, Michel ME (eds) Traumatic head injury in children. Oxford University Press, New York, pp 70–94
5. Bruce DA (2004) Pathophysiological responses of the child's brain following trauma. In: Broman SH, Michel ME (eds) Traumatic head injury in children. Oxford University Press, New York, pp 40–55
6. Brookshire B, Levin HS, Song J et al (2004) Components of executive function in typically developing and head-injured children. Dev Neuropsychol 25:61–83
7. Dikmen SS, Machamer JE, Winn HR et al (1995) Neuropsychological outcome at 1-year post head injury. Neuropsychology 9:80–90
8. Wechsler D (1991) WISC-III. Wechsler intelligence scale for children, 3rd edn. The Psychological Corporation, Harcourt Brace Jovanovich, San Antonio
9. Prigatano GP (2004) The BNI screen for children: Rationale and initial validation studies. Barrow Q 20:27–32
10. Halstead WC (1947) Brain and intelligence. University of Chicago Press, Chicago
11. Fult PA (1981) Fuld object-memory evaluation. Stoelting, Wood Dale, IL
12. Achenbach TM (2001) Child behavior checklist for ages 6–18. ASEBA, University of Vermont, Burlington, VT
13. Kraus JF (1995) Epidemiological features of brain injury in children: Occurrence, children at risk, causes and manner of injury, severity and outcomes. In: Broman SH, Michel ME (eds) Traumatic head injury in children. Oxford University Press, New York, 22–39

Some Keys to Neurorehabilitation Related to the Circuitry of Emotion in the Brain

José León-Carrión

Summary. Emotional disorders are frequent after acquired brain injury and are found in more than 25% to 55% of patients one year after being discharged from hospital. There are four main principles for the rehabilitation of emotional disorders. First of all, the neural correlates of emotional disorders are closely associated with the expression of the disorders. Second, the evolution of emotional disorders is narrowly associated with the evolution of the other deficits sustained by the patient. Third, the pre-morbid emotional and genetic profiles of the patient influence outcome and are very visible in the clinical manifestation. Fourth, use of the combined method of rehabilitation is the best therapeutic option. The Combined Method of Rehabilitation (medication + neuropsychological rehabilitation) of emotional disorders is proposed and described.

Key words. brain injury, neurorehabilitation, emotion, neuropsychological treatment

1 Introduction

Changes in emotional and social behaviour are relatively common following severe traumatic brain injury (TBI), as well as changes in different aspects of personality. In a study by León-Carrión et al [1], the percentage of patients showing significant changes in emotional expressions after sustaining a traumatic brain injury was approximately 60%. The areas assessed, and where changes were observed were irritability (63%), sensation seeking (63%), emotional vulnerability (84%), sociability (42%), and affective indifference (42%). As a group, patients with severe TBI present emotional changes, and when compared to their pre-morbid emotional status, survivors of severe TBI show a significant decrease in sensation-seeking, a marked decrease in sociability and an increase in emotional vulnerability. The latter, emotional vulnerability, is the most frequently observed change in survivors of severe traumatic brain injury.

Department of Experimental Psychology, School of Psychology, University of Seville, C/Camilo José Cela, S/N 41018 Seville, Spain

A study by Bowen et al [2], found that the rate of clinically significant mood disorders is about 38% and that there are associations between emotional state and cognitive and everyday functioning 6 months post-injury. The study by León-Carrión et al [3] shows that 48.6% of their TBI patients fulfil the criteria that classifies them as depressive, and of these, 65% are at clinical risk of committing suicide (33.3% of the total of TBI patients). Another 25.6% do not meet the criteria of depression or suicidal tendencies, and another 25.6% show very low suicidal tendency scores. Only 15.6% of the patients presented depression alone, without risk of suicide. The neurobehavioural and cognitive profile of the TBI suicide-prone patient shows an emotional person with cognitive difficulties in interpreting reality. In these cases, the person tries to understand what is happening around them, but is unable to cope. They show concrete thoughts, although they have difficulty solving problems and have few intellectual resources to cope with their surroundings. They do not know how to distance themselves from the emotional aspects of different situations.

The consequences of emotional impairment after traumatic brain injury lead to psychosocial problems such as decreased social contact, depression, and loneliness, creating a major challenge to community re-entry efforts. Criminal behaviour and violence may, in some cases, be the consequence of head injuries acquired during childhood and youth (gang fights, domestic violence, small blows to the head while driving, falls and so forth) [4]. The social and personal consequences noted in the literature are what made Morton and Wehman [5] recommend that clinicians, such as psychiatric social workers, psychologists or psychiatrists, may need to be called upon more quickly for intervention.

The emotional reaction of patients with TBI is not a simple matter of coping with their new situation. It is also related to the site of the brain lesion and to the genetic profile related to emotions which seems to influence the emotional pre-morbid style of the patient, as well as affect their emotional style after TBI. The reasons that affective disturbances occur following brain injury are complex and may be a direct result of damage to the cortical systems involved with regulating emotion, initiating activities, self awareness, and impulse control. A brief review of the most relevant systems of the brain related to the expression of emotions will be useful in the planning of rehabilitation strategies for these patients.

2 Lesion to Brain Circuitry Producing Emotional Impairment

Rehabilitation strategies for the consequences of brain injury have to take into account the neurological sites producing or controlling emotions or feelings. In the developing of such strategies, the so-called "trigger" of the emotional reaction also has to be considered. Some neuroanatomical sites are associated with the expression of emotions in humans.

The regions of the brain involved in the early processing of affective stimuli, as well as the order of activation of each region, were studied by León-carrión et al using Magnetoencephalography [6]. They found spatiotemporal maps that consisted of two basic components. The first component—involving activation in the occipital and basal aspects of the temporal cortex—lasted 270 ms. post-stimulus on average, and

was found in each subject and in all three conditions. The second component—involving activation in the mesial aspect of the temporal lobes (MTL)—extended from 270 to 850 ms. post-stimulus and was found in all subjects during the unpleasant stimulus condition. After (serial) activating, the mesial temporal lobe structures, or those simultaneous (parallel) to it activated the frontal structures. This activation was most prominent during the unpleasant stimulus condition, but the locus varied across subjects.

These findings are suggestive of a time-locked brain activity associated with emotion with two clear components, one mediating visual recognition of all visual stimuli (both affective and neutral), and the other mediating the generation of emotion itself. The temporal organization of an emotion requires the serial successive and alternating engagement of frontal and posterior cortices in the perception-action cycle, and consists of at least two separate and well-defined components with two clearly distinct and temporally successive patterns of brain activation exhibited by all the subjects.

The basal ganglia facilitate the modulation and motor expression of emotions, moods, needs, and drives. They also facilitate motivation and cognition through corticospinal volitional axial and distal pathways, as well as through limbic motor-visceromotor emotional pathways. Lesions to basal ganglia may lead to emotional lability, a feature of the corticobulbar syndrome, which is frequently found in basal ganglia and vascular dementia, even in the absence of a corticobulbar or bilateral corticospinal syndrome. Anhedonia (loss of pleasure in life) is a frequent finding in Parkinsonism as well as amimia or loss of spontaneous emotional face expression. Lesions to this area of the brain also lead to deficits in emotional communication of speech (motor and sensory aprosodia, syntactic aprosodia).

The limbic system has classically been associated with emotion, and along with the deep temporal lobes has also been reported to store highly charged emotional memories, both positive and negative, which affect motivation and drive. According to Richardson et al [7], the severity of left hippocampal pathology predicted memory performance for neutral and emotional items alike, whereas the severity of amygdala pathology predicted memory performance for emotional items alone. Encoding-related hippocampal activity for successfully remembered emotional items correlated with the degree of left amygdala pathology. Conversely, amygdala-evoked activity with respect to subsequently remembered emotional items correlated with the degree of left hippocampal pathology. Their data indicate a reciprocal dependence between amygdala and hippocampus during the encoding of emotional memories. The principal conclusion from studies of fear conditioning is that the amygdala plays a critical role in linking external stimuli to defense responses [8].

The human prefrontal cortex has been shown to be involved in the experience and appraisal of emotion as well in primary and secondary mood disorders. A study by Damasio [9] found that medial and ventral medial frontal cortex participate in the response to emotion-evoking stimuli. Medial frontal activity seems to be necessary to experience emotion, including depressed mood, anxiety or apathy [10]. No consensus has been achieved, however, regarding the specific location of the prefrontal dysfunction in mood disorders [11]. The orbitofrontal cortex represents one critical structure in a neural system which serves decision making [12]. Decision making, which is influenced by emotion, is not mediated by the orbitofrontal cortex alone, but arises from

large-scale systems that include other cortical and subcortical components. Such structures include the amygdala, the somatosensory/insular cortices and the peripheral nervous system. Studies and observation of emotional expression after frontal cortex damage have indicated a mixed picture: first, overactive emotional expression and emotional experience (hypomanic, aggressive, hypersexual, and uninhibited expression; obsessive-compulsive behavior); second, erratic and underactive emotional expression and emotional experience (lability, blunted affect, akinetic-mutism, apathy).

Some authors [13] have suggested that the frontal lobe may be a major neural substrate influencing emotional reactivity and indicate two different temperament patterns: predominant left frontal activation and predominant right frontal activation. In the former, people experience more intense positive affect and less intense negative affect to positive and negative emotional stimulus, respectively. In the latter, individuals show the reverse pattern of emotional reactivity. Rolls et al [14] found that a group of patients with damage to the ventral part of the frontal lobe was severely impaired when compared to a group of patients without damage to this area (the non-ventral group) in the reversal and extinction of simple visual discrimination tests. In these tests, they continued to make responses to a previously rewarded stimulus, reflecting the degree of uninhibited and socially inappropriate behaviour exhibited by patients. Frontal patients have difficulty in modifying responses, especially when followed by negative consequences, what may contribute to the inappropriate behaviour shown in daily life by patients with frontal lobe damage.

Paradiso et al [11] examined mood and behaviour changes after frontal damage in patients with single lateral and single medial frontal lesions. They found that DSM IV major depressive and generalised anxiety disorders were more frequent in patients with lateral lesions than in those with medial lesions at 2 weeks. But at 3 months, patients with lateral damage showed greater severity of depressive symptoms, and greater impairment in both activities of daily living and social functioning. At initial evaluation, depressed mood and slowness were more frequent, whereas at 3 months slowness, lack of energy, and social unease were more frequent in the lateral than the medial group. Patients with lateral lesions showed greater reduction of emotion and motivation (apathy) during both examinations. Medial frontal injury may fail to produce emotional dysregulation or may inhibit experience of mood changes, anxiety, or apathy. They also found that lateral prefrontal damage may disrupt mood regulation and drive while leaving intact the ability to experience (negative) emotions.

The thalamus has complicated bidirectional and sometimes unidirectional connections with cortical structures of the cerebral hemispheres, cerebellum, hypothalamus, and many brainstem nuclear structures. Almost all incoming information passes through the thalamus before finally reaching cortical destinations. Typical patients show no emotional reaction and remain unconcerned about things happening around them, even when they are of personal importance. Sometimes this apparent apathy is mixed with irritability. Euphoria may also emerge after bilateral mediodorsal nuclei damage, often accompanied by attentional and/or cognitive impairment [15]. Some behavior appears similar to that of frontal disorders: uninhibited or extremely inappropriate behavior, such as urinating on the floor without embarrassment; childish behavior and euphoria; hyperphagia or bulimia; voracious and indiscriminate drinking without becoming satiated. Studies on neocortical contributions to emotional pro-

cessing by Borod [16] found that right cerebral hemispheric is dominant for emotion, regardless of valence and channel, but that this dominance is more consistent in perception than in expression. When lesion site is a factor, posterior sites are important for perception and anterior sites are important for expression.

3 Strategies for the Treatment of Emotional Impairment after Acquired Brain Injury

The more subcortical the source of the emotion, the more difficult it becomes to penetrate cognitively, and the more difficult it will be to treat: brainstem, diencephalic, limbic. The greater the cortical component of the emotion, the easier it will be to treat psychologically: frontal, temporal. Feelings are cortical and emotions are more subcortical, which is why feelings are easier to treat than emotions. But remember, feelings are not always true, so if you treat a false feeling as a real one, the underlying emotion remains. The more primary the emotion, the greater the need for adequate pharmacological intervention to control it. Pharmacological intervention does not exclude psychological intervention. It is better to make use of both strategies. Some authors and our experience recommend that treatment should begin as soon as the problem is observed.

A treatment program for emotional disorders for people with brain injury should emphasize the following [17]: location of damaged areas, gradation of cognitive treatment, personalized psychotherapeutic treatment, group therapy, family counselling, daily life activities, and evaluation of the costs/benefits of pharmacological intervention. To accomplish this, we recommend what we call the Combined Method [18,19].

The Combined Method is the use of both pharmacological and neuropsychological strategies in the design of rehabilitation programs for acquired brain injury patients. The Combined Method is a methodological engineering process, combining knowledge of the intact and non-intact functional brain with cognition, emotion, behavior and neuropharmacology. The result is a new functional cerebral reorganization which allows the patient to have psychological and social coherence. With the Combined Method, it is important to know both the pharmacodynamics of emotion as well as neuropsychological rehabilitation strategies.

When planning rehabilitation, one has to take into account that patients with brain injury are more sensitive to the side effects of medications, especially psychotropics. Doses of psychotropics must be prudently increased, minimizing side effects: start slow, go slow [20]. Patients with TBI and emotional disorders taking medication must be reassessed frequently in order to avoid side effects, monitor the evolution of emotional expressions and check the effect of medication on cognition. In cases requiring liver function tests, these should be obtained every three months.

The selection of appropriate medication to treat emotional disorders has to be guided by their side effects profile and their effects on cognition (i.e.: sedative effects, memory disturbances, sexual dysfunction, etc.). The possibility that an individual may consider or attempt suicide following a traumatic brain injury has been identified as a critical factor to be examined in neuropsychological rehabilitation programs. Several published studies suggest that changes in the serotonin (5HT) system and to the ventral prefrontal cortex are the neurobiological abnormalities most consistently

associated with suicide [21–23]. Other studies have shown that dysregulation of the hypotalamic-pituitaty-adrenal (HPA) axis can be found in suicide victims. The HPA is the neuroendocrine system that responds to stress and whose final product, corticosteroids, targets components of the limbic system, particularly the hippocampus [24]. The use of medication that can reduce the stress response, and/or decrease HPA activation, will be useful in the pharmacological treatment of anxiety, depression, and perhaps, in suicidal behavior [25].

4 Concluding Remarks and Prospective

Treatment of emotional and affective disorders should be directed, from the start, towards supporting the patient's basic necessities. Reality adjustment therapies should be favored over interpretative or figurative therapies of reality. In therapy, reality should be clear. Therapy should favor "awareness with hope" and not confusion. It should seek out the patient's strong side, those qualities and abilities which are best preserved, what he or she does best, and reinforce this. From this central point, the therapy can expand into other areas. Rehabilitators have to find points and areas to enhance motivation and help the patient to develop the expression of emotions that are socially adequate, not socially disabling.

The future is today, when pharmacogenomics contribute to individualize drug choice together with psychotherapy by using genotype to predict positive clinical outcomes, adverse reactions, and levels of drug metabolism in patients with traumatic brain injury showing adverse emotional reactions and experiences.

Acknowledgements. This Project has been funded by the Ministry of Science and Education, as part of the National Plan for Scientific Research, Development and Technological Innovation (2004–2007), and co-funded by the European Fund for Regional Development (FEDER): FIT-300100-2004-58.

References

1. León-Carrion J, Madrazo M, et al (1999) Emotional changes following severe brain injury (Cambios emocionales después de un traumatismo craneoencefálico grave). Span J Neuropsychol (Revista Española de Neuropsicología) 1:75–82
2. Bowen A, Neumann V, Conner M, et al (1998) Mood disorders following traumatic brain injury: Identifying the extent of the problem and the people at risk. Brain Inj 12:177–909
3. Leon-Carrion J, De Serdio-Arias ML, Cabezas FM, et al (2001) Neurobehavioural and cognitive profile of traumatic brain injury patients at risk for depression and suicide. Brain Inj (2):175–181
4. León-Carrión J, Chacartegui Ramos FJ (2003) Blows to the head during development can predispose to violent criminal behaviour: rehabilitation of consequences of head injury is a measure for crime prevention. Brain Inj 17:207–216
5. Morton MV, Wehman P (1995) Psychosocial and emotional sequelae of individuals with traumatic brain injury: a literature review and recommendations. Brain Inj 1:81–92
6. Leon-Carrion J, Papanicolaou A, Castillo E (in press) Time-locked brain activity associated with emotion

7. Richardson MP, Strange BA, Dolan RJ (2004) Encoding of emotional memories depends on amygdala and hippocampus and their interactions. Nat Neurosci 3:278–285
8. LeDoux J (2003) The emotional brain, fear, and the amygdala. Cell Mol Neurobiol 23:727–738
9. Damasio A (1995) On some functions of the human prefrontal cortex. In: Grafman J, Holyoak KJ, Boller F (eds) Structure and function of the human prefrontal cortex. Ann N Y Acad Sci 769:241–251
10. Fuster J (1997) The prefrontal cortex. Anatomy, physiology, and neuropsychology of the frontal lobe, 3rd edn. Lippincot-Raven, Philadelphia
11. Paradiso S, Chemerinski E, Yazici KM, et al (1999) Frontal lobe syndrome reassessed: Comparison of patients with lateral or medial frontal brain damage. J Neurol Neurosurg Psychiatry 67:664–667
12. Bechara A, Damasio H, Damasio AR (2000) Emotion, decision making and the orbitofrontal cortex. Cerebral Cortex 10:295–307
13. Davison RJ, Irwin W (1999) The functional neuroanatomy of emotion and affective style. Trends Cogn Sci 3:11–21
14. Rolls ET, Hornak J, Wade D, et al (1994) Emotion-related learning in patients with social and emotional changes associated with frontal lobe damage. J Neurol Neurosurg Psychiatry 57:1518–1524
15. Stuss DT, Levine B (2002) Adult clinical neuropsychology: Lessons from studies of the frontal lobes. Annu Rev Psychol 53:401–433
16. Borod JC (1992) Interhemispheric and intrahemispheric control of emotion: A focus on unilateral brain damage. J Consult Clin Psychol 60:339–348
17. León-Carrión J (1997) An approach to the treatment of affective disorders and suicide tendencies after TBI. In: León-Carrión J (ed.) Neuropsychological rehabilitation: Fundamentals, innovations, and directions. GR/St. Lucie Press, Delray Beach, FL, p 419
18. Leon-Carrion J, Dominguez-Roldan JM, Murillo-Cabezas F, et al (2000) The role of citicholine in neuropsychological training after traumatic brain injury. NeuroRehabilitation 14:33–40
19. León-Carrión J (2005) Rehabilitation of cognitive disorders after acquired brain injury: The Combined Method (TCM). In: León-Carrión J, Zitnay G, von Wild K (eds) Brain injury treatment: theories and practices. Taylor and Francis, London (in press)
20. Yudofsky SC, Silver JM, Hales RE (1990) Pharmacologic management of aggression in the elderly. J Clin Psychiatry 51:33–39
21. León-Carrión J (1997) Neuropsychological rehabilitation: Fundamentals, innovations, and directions. St. Lucie Press, Delray Beach, FL
22. Mann JJ (1987) Psychobiologic predictors of suicide. J Clin Psychiatry 48:39–34
23. Mann JJ, et al (1987) Evidence for the 5-HT Hypothesis of suicide: A review of postmorten studies. Br J Psychiatry 155:7
24. Lopez J, et al (1997) Regulation of 5-HT receptors and the hypotalamic-pituitary-adrenal axis: Implications for the neurobiology of suicide. In: Stoff DM, Mann JJ (eds) The neurobiology of suicide: from the bench to the clinic. Ann N Y Acad Sci 836:106
25. Thomas DF, León-Carrión J (2005) Diagnosing and treating affective disorder after Brain injury. In: León-Carrión J, Zitnay G, von Wild K (eds) Brain injury treatment: Theories and practices. Taylor and Francis, London (in press)

Multidisciplinary Treatment for Trauma —The AMN View

KLAUS R. H. VON WILD

Summary. Prospective analysis of 6,800 acute TBI confirmed the incidence of TBI is 320/100,000 population in the rich countries. Mental-cognitive impairments are both more persistent and constitute more of a handicap than physical and focal neurological disabilities. In Europe there are about 300,000 paraplegics and in every country approximately 1,000 new cases of SCI every year. Figures of TBI ands SCI are increasing due to insufficient social economic situations. Multidisciplinary Neurotraumatology focuses at 6 main issues: In the first place the "silent epidemic" TBI. Secondly functional recovery patients after SCI. Re-engineering for locomotion was successful (1) using an implant of Neuromedics that contains the ASIC chip (Neuromedics, Montpellier, France) for locomotion during FES, and (2) by CNS-PNS connection, a reconstructive surgical by-pass procedure to the hip muscles (BRUNELLI paradigm). Thirdly: holistic functional rehabilitation targeted at victims social reintegration. Fourth issue: Quality management that is dependent on (1) the budget of a given social-healthcare system in relation to political economy, (2) respect of guidelines and evidence based medicine, (3) education and (4) research activities. Fifth issue: architecture of hospitals and rehabilitation centres should provide functional value combined with an atmosphere for humane interrelation. Sixth the most sensitive issue: Social healthcare ethics and morals in neurotrauma including medical decision making of withdrawal of nutrition and hydration The purpose of the AMN is the advancement of Neurotraumatology in research, practical application and teaching to be obtained by a multidisciplinary approach and cooperation of all specialists, scientific investigators, therapists, politicians, care providers and care-givers on an academic basis.

Key words. interdisciplinary team approach, multiprofessional management of TBI and SCI, re-engineering of brain and spinal cord lesions, restoration of locomotion, functional rehabilitation in neurosurgery, quality of life

---

Professor of Neurosurgery, Medical Faculty, Westf. Wilhelms-University, Münster, NRW; Professor of Neurorehabilitation and Re-engineering of brain and spinal cord lesions, International neuroscience Institute, Hannover; Director kvw-neuroscience consulting GmbH, 32 Frauenburgstrasse, D-48155 Münster, Germany

1 Introduction

The World Academy of Multidisciplinary Neurotraumatology (AMN) was established in 2003 on initiative Prof Tetsuo Kanno [40]. Like others he has realized the situation concerning acute neurotrauma care and functional rehabilitation in the eastern and the western hemisphere and he wanted to open up a platform for scientific education, communication, scientific exchange, and research on neurotrauma around the world. He had experienced such a cooperation regarding neurosurgery in Asia respectively for Neurotraumatology in Europe working with the Euroacademia multidisciplinaria neurotraumatologica (EMN) The EMN academicians are using a multiprofessional academic approach for the advancement of neurotrauma in research, practical application and teaching [1,2,32,34,44]. Neurotraumatology is a major burden for the social-economic and health- care systems around the world, despite the fact that the field of neurotrauma has made remarkable strides over the past three decades [2–9]. Figures of CCI and SCI victims are increasing, predominantly in the poor countries, while in the rich countries quality management in neurotrauma and legal accident prevention measures have reached a remarkable high standard that is reflected by the improvement of early functional outcome and final social reintegration and quality of life [36,42]. In contrast in the poor countries this situation got even worse despite all efforts.

Although much irreversible damage to the brain and spinal cord occurs immediately during the impact, neurosurgeons who became more and more involved in acute neurotrauma care and surgical treatment have noticed the cascade of evolving destructive processes over the following hours and days and the risks and consequences of concomitant multiple organ lesions and impending secondary complications that worsen the ultimate outcome [8,9]. They were educated and so they respect the pathophysiology following neurotrauma and are aware of the consequences of "silent secondary insults" after acute trauma as they were stressed by several groups, for example by the late J. Douglas Miller [8] for craniocerebral injury (CCI) and Charles H Tator [10] for spinal cord injury (SCI). Much progress has been made in understanding these secondary insults at the clinical level as well as the biochemical level. Efforts of neurotrauma specialists and scientific investigators have always resulted in a growing awareness of the need to provoide supportive care for neurotrauma patients, but if the problem is to be attacked scientifically there is a need for more of those with experience in the brain and spinal cord to take more active interest in the process of functional recovery [11]. "A scientific approach does not imply waiting for experimentalists to take the lead: phylogenetic differences in the organization of the higher nervous system inherently limit their contribution. The proper study for the mankind is the man"! quotation of a statement of Bryan Jennnett, 1975 [12, p 4] Since that time as a result neurosurgeons and other specialists who became more involved in the challenging field of neurotrauma and they are more interested in the acute surgical and conservative intensive care treatment of patients after CCI and SCI. When evidence based medicine came into the focus of medical interest international and national Guidelines have been published to standardize best medical practice also in neurotrauma. Prospective and controlled multiple centre studies were performed to proof quality management and the efficiency of acute neurosurgical treatment. Posttraumatic neurorehabilitation, however, has still not really come to the

neurosurgeons attention. For example EBIC, who published guidelines on acute TBI treatment, focused its activities on brain protection after CCI analysing, by guiding prospective clinical studies, acute neurosurgical care and early outcome after CCI and the beneficial effects of drugs [9,13,14]. This was of course in close cooperation with researchers, the pharmaceutical industry and clinicians. Clinicians who initially generated interest in the areas of acute trauma care and who are now much better educated in the scientific process started to work together with basic scientists who would otherwise have hesitated to be confronted with the trauma victims (Narayan et al 1995) The need for a multidisciplinary approach to neurotrauma is evident [15–27].

2 Results

2.1 First Issue: Quality Management in CCI

We have analysed the data on quality management of 6,783 patients after acute CCI within one year in a prospective, controlled population based, multicentre study for tow defined regions in Germany: Hannover (industrialized) $N = 5,643$ and Münster (rural) $N = 2,140$ The social outcome of 4,307 (= 63.5%) was assessed by telephone interview after one year. The CCI patients were admitted to 40 hospitals as follows: general and trauma surgery = 78%; paediatric surgery = 8%; maxillo-facial = 7%; neurosurgery and paediatrician = 3.6%; neurology = 1.4%; ENT = 6%; internal = 0.5%; other 2.2%; missing data 1%. Following emergency examination 5,221 CCI (77%) were hopsitalized (Table 1) Emergency primary imaging diagnostics after acute TBI 1. Plain x-ray images of the skull were taken in 5,507 (= 82%) of cervical spine in 1,377 patients (= 20%); other imaging diagnostics were performed in 2,986 (= 43.6%), no imaging diagnostics being conducted in 806 patients (= 12%).

2. Cranial computerized tomography of the head and skull (CCT) was performed in 1,300 patients (= 19.2%) during the emergency examination compared with 1,216 patients (= 23.3%) CCT out of 5,220 at the beginning of medical treatment in the hospital. Initial body CT scans were done in only 80 patients (= 1.2%.)

TABLE 1. Causes and severity of CCI (GCS) at emergency hospital admission

GCS/CCI severity	Mild	Moderate	Severe	Not assessed	Patients
Traffic accident	841	47	113	772	1.773
	84%	4.7%	11.3%	–	100%
Leisure time	1.257	50	36	1.054	2.397
	93.5%	3.7%	2.6%	–	100%
At work	524	16	14	457	1.011
	94.6%	2.9%	2.5%	–	100%
At home	1.023	41	41	913	2.018
	92.6%	3.7%	3.7%	–	100%
No special cause	3	1	1	23	28
	60	20%	20%	–	100%
No data	5	1	–	54	60
	83%	17%	–	–	100%
All	3.395	145	191	3.052	6.783
	90.9%	3.9%	5.2%	45%	100%

Cranial magnetic resonance imaging (MRI) was performed in nine patients (= 0.1%). Emergency concomitant (multiple) organ lesions were frequently diagnosed: maxillo facial in 58.7%; cervical spine = 8.8% and thoracic or lumbar spinal = 2.6%; thorax = 7.2%; abdomen = 2.6%, pelvic = 3.4%. Others lesions were complained in 19.6%. CCI severity, however, was only assessed in 55% of all CCI. CCI severity was classified as being "mild" in 91%, "moderate" in 4%, and "severe" in 5% of patients when examined in the emergency room (Table 1).

Despite the intensity of traumatic brain lesion and the functional impairments only 258 patients (= less than 5%) received posttraumatic neurorehabilitation on an inpatient basis (Table 2a). These were in mainly in the institutions for early neurosurgical rehabilitation in Münster (the authors unit, specially designed architecture) and in a 70km distant common rehabilitation institute for Hannover area (Table 2b).

TABLE 2a. Functional impairment after CCI, long term and early posttraumatic rehab.

CRS at admission	Patients for rehabilitation	Patients for ENNR
<10/24	25	19
	14.3%	22.1%
9–19/24	37	19
	21.1%	22.1%
20–23/24	24	11
	13.7%	12.8%
24/24	89	37
	50.9%	43.0%
Total	175	86
%	100.0%	100.0%
No data	83	14
Patients	258	100

TABLE 2b. Coma remission scale score of CCI at admission to the post acute and early rehabilitation institute

CRS at admission	Patients admitted for rehabilitation $n = 258$			Patients admitted for ENNR $n = 100$		
	MS	H	Else	MS	H	Else
<10/24	14	7	4	14	2	3
	21.2%	9.7%	10.8%	22.2%	12.5%	42.8%
9–19/24	10	24	3	9	9	1
	15.2%	33.3%	8.1%	14.3%	56.3%	14.3%
20–23/24	7	12	5	7	3	1
	10.6%	16.7%	13.5%	11.1%	18.8%	14.3%
24/24	35	29	25	32	2	2
	53.0%	40.3%	67.6%	50.8%	12.5%	28.6%
Total	66	72	37	63	16	7
%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
No data	2	10	71	1		13
Patients	68	82	108	64	16	20

TABLE 3. Discharge after hospital treatment and CCI severity according to initial GCS

Discharge/CCI severity	Mild	Moderate	Severe	No data	Patints
Home with special	3.576	272	2	75	3.925
recommendations	91.1%	6.9%	0.1%	1.9%	100.0%
Home without	695	45	1	8	749
recommendations	92.8%	6.0%	0.1%	1.1%	100.0%
Early neuro-rehabilitation	14	8	2	45	69
	20.3%	11.6%	2.9%	65.2%	100.0%
Rehabilitation	**108**	**47**	**2**	**27**	**184**
	58.7%	**25.5%**	**1.1%**	**14.7%**	**100.0%**
Other hospital	59	12	1	14	86
(no rehabilitation)	68.6%	14.0%	1.2%	16.2%	1.6%
Nursing home	93	15	1	4	113
	82.3%	13.3%	0.9%	3.5%	100.0%
Home care (completely	17	**2**	–	–	**19**
dependent)	**89.5%**	**10.5%**			**100.0%**
Death	**6**	–	–	**38**	**44**
	13.6%			**86.4%**	**100.0%**
Missing data	13	4	0	15	32
	40.6%	12.5%		46.9%	100.0%
Total number	4.581	405	9	226	5.221
	87.7%	7.8%	0.2%	4.3%	100.0%

Referred were 115 patents with mild, 41 with moderate and 19 with severe CCI (Table 3) The early outcome was as anticipated.

2.2 Second Issue: Re-Engineering in SCI

Paraplegia means a live long sentence of sensory loss, paralysis and dependence. We were involved in two different projects to restore voluntary locomotion in parapelegs.

2.2.1 SUAW [28]

We took part in a still experimental European clinical project aimed at restoration of locomotion by implanted electrical stimulation to stand up an walk again (SUAW) [28]. The novel implant with an ASCI-x Chip had 16 channels to be connected with bipolare and monopolar electrodes for the FFS of the hip muscles with special discrimination of the time, the intensity and electrical power. The first implantation in a 38 years paraplegic man, in 1999, was the result 10 years intensive research work of a transdisciplinary/multidisciplinary group of trauma,-neurological, orthopaedic, hand- and plastic reconstructive surgeons, electro- technicians, physiotherapists and scientific investigators from six clinic centres for rehabilitation, six surgical departments of the medical faculties of six countries, and fife institutes for biotechnology research. After six years this patient can still use his computer for standing and walking but in our second patient we had to remove the implanted device because of

an infection following the repair of one slipped electrode after one year of functioning. Our project is continued by the functional anatomist and specialist in robotics Pierre Rabischong, Medical Faculty Montpellier, France.

2.2.2 CNS-PNS Connection (the BRUNELLI Paradigm) [29]

Giorgio A. Brunelli, orthopaedic, trauma, and handsurgeon and the author met during the SUAW project. We have performed the two implantations of the EFS devices together with B. Benichou, hand—and plastic surgeon, Centre Propara, Montpellier, France under the supervision of Kris Krishnan, Neurosurgeon and Rehabilitation physician European Calies Association, University of Aalford, UK. G.A.B became actively involved in the experimental clinical project of central nervous system (CNS) and peripheral nervous system (PNS) connection with aid of surgical reconstructive by-pass procedure in the early eighties that became known as *Brunelli Paradigm*. We applied this technique since 2000 in three paraplegic and otherwise healthy patients after complete traumatic thoracic cord avulsion. Re-innervations of distally connected hip muscle groups for functional restoration of locomotion needs more than 18 months [29]. The first patient can walk again with sticks by herself, climbing the stairs and swims, as it was demonstrated in the video. The time interval in the other two patients is still to short for functional recovery.

2.3 Third Issue: Holistic Functional Rehabilitation [17,30]

It has become obvious that it is more the mental-cognitive and neurobehaviuoral impairment than the physical or localized neurological impairment that influence the patient's social re-integration and quality of life after neurotrauma [41]. Guidelines and recommendations for quality management of neurotrauma do not focus on the need for proper rehabilitative interventions to improve impaired higher cerebral cognitive functions [1,15,18,19,23]. Our concept of Neurosurgical rehabilitation follows the guidelines of the German Task Force that we worked out together with neurologists, neurosurgeons, rehabilitation physicians, paediatricians and neuropsychologist and published in 1993 [16,27,32,34]. It became accepted by the politicians, care providers and care givers as well as by the doctors and the rehabilitation personnel and has been introduced into the German social and health care system in 1994. Our special unit has been realized ten years ago according our guidelines [31,32]. It is as a pilot project of the Government of NRW. The study results mentioned above for CCI confirm the efficiency and the effectiveness of quality management for functional recovery after CCI in every sense. Functional recovery of impaired physical and cognitive functioning over time can be reliable assessed during early neurological neurosurgical rehabilitation with aid of the 24 points Coma remission Scale score that was worked out and established by our Task Force (Table 2**a,b**) and has been translated in English [27].

2.4 Fourth Issue: Education and Research [9,12,13,15,20,23,26]

There is clear evidence that the early outcome in patients after CCI was significantly improved when neurosurgeons became interested in Neurotraumatology and took over the responsibility for intensive care treatment and emergency evacuation of

intracranial haematoma after introduction of CCT [33]. Clinicians who became interested I neurotrauma care started educational programmes and established multidisciplinary research projects and they established for CCI and SCI data banks as well as international cooperative studies. To day transdisciplinary emergency teams take care of the victims [13,25,33,34], so that only life threatening multiple organ lesions, for example in polytraumat thoracic and/or vascular and abdominal lesions will be immediately operated, while other lesions are postponed focussing on brain protection with oxygen supply, stable cerebral blood perfusion and normal ICP values to preserve brain plasticity for recovery of higher cortical functions. It has further been demonstrated and was confirmed in our prospective study that a "mild" CCI may cause severe functional impairments [26,35]. Therefore we have published the EFNS guidelines for management of mild TBI for the neurological societies in Europe [35].

2.5 Fifth Issue: Humane Architecture

When looking, for example, at the seven rehabilitation centres of Sahra Network in Brasilia that were built on Aloysio Campos da Paz Jr initiative, M.D., Professor of orthopaedics and rehabilitation, Diretoria da Rede SARAH de Hospitais Brasiali, Brasil, it is obvious that humane architecture can meet the special interests and needs of patients after brain and spinal cord lesions as long as the people who are responsible for those projects cooperate in a multidisciplinary way. This is also exemplarily demonstrated by Lippo Karawaci New Town, a Jakarta Edge City, Indonesia, planned and managed and technical audit by Gordon G. Benton, Member of the Royal Institute of British Architects, RIBA, reflecting an cultural based architecture of the hospital and respect the needs of psychologically stressed TBI and SCI patients by providing functional value combined with an atmosphere for humane interrelation. Both gentlemen are Academicians of AMN. There are many more examples including our special unit for neurosurgical early rehabilitation in Münster [32].

2.6 Sixth—The Most Sensitive Issue: Ethics and Morals and Quality of Life after Trauma [20,30,36]

There is on ongoing discussion concerning medical decision making in regard to end of life and organ transplantation around the world. These topics are approached from different sites and working parties involved [20]. In this context I would like to refer without any further commend on the Declaration of Helsinki of the world medical association (WMA) adopted by the 18th WMA general assembly Helsinki 1964, latest amendment 852nd WMA assembly Edinburgh 2000. One has to agree that cultural based medicine (this term was introduced by Prof Dr. Tomio Ohta, Osaka, Bali Dec. 2004) plays a major role and should to be respected more in the future because of its influence concerning medical decision making in any case, especially in patients suffering from the severest functional impairments of higher cortical functions, in a vegetative state (apallic syndrome) for years without symptoms and signs of recovery. But how to assess quality of life? *Qolibri*, a specific measure to assess health related quality of life in persons after CCI was worked out by a multidisciplinary European

working group since 1999 [36] and was presented at the 3rd AMN in Nagoya March 10, 2005.

3 Discussion

Quality management in neurotrauma care requires special awareness of the problems and education, the willingness for cooperation, in an academic way, with scientific investigators to understand and to handle the medical problems to improve the patients final social outcome. Neurosurgeons should become involved and have to participate actively in the discussions that are related to the main problems within all fields of Neurotraumatology, for example, social health care, ethics and morals, cultural based medicine, robotic, functional imaging, neurointensive care, neurorehabilitation, research, functional recovery, biotechnology, re-engineering of brain and spinal cord lesions [29], accident prevention, education, gerontology, economics, and many others. The six issues that were addresses above are typical examples where multidisciplinary cooperation is needed.The purpose of the AMN, therefore, is to be attained by, in particular the organisation of international congresses as well as participation in such events including regional and national workshops and educational meetings and commitment to excellence in education through organisations of workshops and intensification of cooperation with scientific academies, societies, associations as well as research institutions and companies who are concerned with questions related to neurotrauma.

4 Conclusions

A multidisciplinary and academic approach with close cooperation of all people involved in the broad field of Neurotraumatology offers a novel avenue for a still better outcome of patients after CCI and SCI with impaired higher cerebral functioning. The AMN might help understanding and solving some of the problems. The *Academia Multidisciplinaria Neurotraumatologia* (AMN) is not a society. World Academy of Neurotraumatology should consist of individuals that are actively collaborating on a multidisciplinary/interdisciplinary research and/or teaching in Neurotraumatology. That is, people being invited to join this academic group should be involved in doing these activities with a given member of the Academy and their level of performance would really have to meet high standards of scholarship (G. Prigatano, President, February 2005) For more information please visit: www.neurotraumaworldamn.org

Acknowledgment The author thanks Paul Wenzlaff for his assistance of analysing and providing the statistical data of the TBI study in cooperation with E. Rickels and the TBI Study Council and Centre for Quality Management in Healhcare, Medical Association of Lower Saxony, Hannover, Germany.

Part of the data presented in this article belongs to (1) the work on *Quality Management in Traumatic Brain Injury (TBI)* that was granted by Kuratorium ZNS and Hannelore Kohl donation, Bonn, and Cerebprotect Münster; Germany, (2) the *SUAW* project granted under the BIOMED II Programme European community and (3) the

CNS-PNS paradigm work granted by the Italy Foundation for Research on Speinal Cord Lesion Brescia, Italy functioning.

References

1. Arbeitsgemeinschaft Intensivmedizin und Neurotraumatologie der DGNC (1997) Leitlinien zur Primärversorgung von Patienten mit Schädel-Hirn-Trauma. Zbl Neurochir 58:13–17
2. von Wild KRH, Nordström CH, Hernández-Meyer (eds) (1998) Pathophysiological principles and controversies in neurotrauma care. W Zuckschwerdt Verlag, Munich
3. Baethmann A, Wirth A, Chapuis D, et al (2000) A system analysis of the pre- and early hospital care in severe head injury in Bavaria. Restor Neurol Neurosci 16:1
4. Berger E, Leven F, Pirente N, et al (1999) Quality of life after traumatic brain injury: A systematic review of the literature. Restor Neurol Neurosc 14:93–102
5. Bouillon B, Raum M, Fach H, et al (1999) The incidence and outcome of severe brain trauma —design and first results of an epidemiological study in an urban area. Restor Neurol Neurosci 14:85–92
6. Kraus JF, McArthur DL, Silverman TA, et al (1996) Epidemiology of brain injury. In: Narayan RK, Wilberger JE Jr, Povlishock JT (eds), Neurotrauma. McGraw-Hill, New York, pp 13–30
7. Narayan RK, Wilberger J Jr, Povlishock JT (eds) (1995) Neurotrauma. McGraw-Hill, New York
8. Miller JD, Piper IR, Jones PA (1995) Pathophysiology of head injury (chapter 5). In: Narayan RK, Wilberger J Jr, Povlishock JT (eds) Neurotrauma. McGraw-Hill, New York, pp 61–69
9. Teasdale GM, Graham DI (1998) Craniocerebral trauma: Protection and retrieval of the neuronal population after injury. Neurosurgery 43:723–737
10. Tator CH (1995) Classification of spinal cord injury based on neurological presentation. In: Narayan RK, Wilberger J Jr, Povlishock JT (eds) (1995) Neurotrauma. McGraw-Hill, New York, pp 1059–1073
11. Stein DG (2000) Brain injury and theories of recovery. In: Christensen AL, Uzzell BP (eds) International handbook of neuropsychological rehabilitation. Kluver Academic Plenum Publishers, New York, USA, pp 9–32
12. Jennett B (1975) Scale, scope and philosophy of the clinical problem. In: The Ciby Foundation (ed.) Outcome of severe damage to the central nervous system. Elsevier, Excerpta Medica North Holland, Amsterdam, Oxford, New York, pp 3–21
13. Maas AIR, Dearden M, Teasdale GM, et al on behalf of the European Brain Injury Consortium (1997) EBIC guidelines for management of severe head injury in adults. Acta Neurochir (Vienna) 139:286–294
14. Murray GD, Teasdale GM, Braakman R, et al on behalf of the European Brain Injury Consortium (1999) The European Brain Injury Consortium survey of head injuries. Acta Neurochir (Vienna) 22:223–236
15. Brain Trauma Foundation Inc (ed.) (1995) Guidelines for the management of severe head injury. A joint initiative of the American Association of Neurological Surgeons & the Brain Trauma Foundation. Copyright 1995 by the Brain Trauma Foundation, Inc. USA
16. Voss A, Ortega Suhrkamp E, von Wild K, et al (1993) Bundesarbeitsgemeinschaft medizinisch-beruflicher Rehabilitations-Zentren Phase II Empfehlungen der Arbeitsgemeinschaft Neurologische-Neurochirurgische Frührehabilitation. Issue 8, March 1993
17. Christensen AL, Uzzell BP (eds) (2000) International handbook of neuropsychological rehabilitation. Kluwer Academic/Plenum Publishers, New York, Boston, Dorfdrecht, London, Moscow

18. Deutschen Gesellschaft für Neurochirurgie und Deutschen Gesellschaft für Anästhesiologie und Intensivmedizin sowie der Deutschen Interdisziplinären Vereinigung für Intensiv- und Notfallmedizin DIVI (eds) (1997): Emptchlunger zur Primärversorgung von Patienten mit Schädel-Hirn-Traumen. Notarzt 13:45–48 (www.divi.org.de)
19. Fernandez R, Firsching R, Lobato R, et al (1997) Guidelines for treatment of head injury in adults. Zbl Neurochir 58:72–74
20. Gigli GL, Zasler ND (guest eds) (2004) Life—sustaining treatments in vegetative state: The scientific advances and ethical dilemmas. Neurorehabilitation 19:4
21. 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. In: von Wild KRH (ed.) Functional rehabilitation in neurosurgery and Neurotraumatology. Acta Neurochir (Vienna) [Suppl] 79:37–39
22. Kanno T, Kamel Y, Yokoyama T, et al (1989) Effects of dorsal spinal cord stimulation (DCS) on reversibility of neuronal function-experience of treatment for vegetative states. Pace 12:733–738
23. Kawasny O, Kemetzhofer P, Fialka C, et al (1999) Guidelines for prehospital care of patients with severe head injury. Acta Chir Austriaca 31 [Suppl]:27–29
24. Neugebauer E, Lefering R, Noth J (guest eds) (1999) Neurotrauma and plasticity. Rest Neurol Neurosci 14:3
25. Schuhmann MU, Rickels E, Rosahl SK, et al (2001) Acute care in neurosurgery: Quantity, quality, and challenges. J Neurol Neurosurg Psychiatry 71:182–187
26. Servadei F, Teasdale G, Merry G on behalf of the Neurotraumatology Committee of the World Federation of Neurosurgical Societies (2001) Defining acute mild head injury in adults: A proposal based on prognostic factors, diagnosis, and management. J Neurotrauma, 8:657–663
27. von Wild KRH (2000) Perioperative management of severe head injuries in adults. In: Schmidek H, Sweet WH (eds) Operative neurosurgical techniques: Indications, methods, and results, 4th edn. Saunders Company, Philadelphia, PA, pp 45–60
28. von Wild KRH, Rabischong P, Brunelli G, et al (2001) Computer added locomotion by implanted electrical stimulation in paraplegigc patients (SUAW). Acta Neurochir Suppl 79:99–104
29. von Wild KRH, Brunelli GA (2003) Restoration of locomotion in paraplegics with aid of autologous bypass grafts for direct neurotisation of muscles by upper motor neurons- the future: Surgery of the spinal cord? Acta Neurochir Suppl 87: 107–112
30. Ben-Yishay Y, Daniels-Zide E (2000) Examined lives: Outcome after holistic rehabilitation. Rehabil Psychol 45:112–129
31. Ortega-Suhrkamp E, von Wild KRH (2002) Standards of neurological-neurosurgical rehabilitation. Acta Neurochir (Vienna) [Suppl] 79:11–19
32. von Wild KRH (2001) Neurorehabilitation—a challenge for neurosurgeons in the 21st century. Concepts and visions of the WFNS Committee on neurosurgical rehabilitation. Acta Neurochir Suppl 79:3–10
33. Trooskin S, Copes WS, Bain LW, et al (2004) Variability in trauma center outcomes for patients with moderate intracranial injury. J Trauma 57:998–999
34. Ortega-Suhrkamp E (2001) Early functional outcome in isolated (TBI) and combined traumatic (CTBI) brain injury. Acta Neurochir (Vienna) [Suppl] 79:31–32
35. Vos PE, Battistin L, von Wild KRH, et al (2002) EFNS Guidelines on mild traumatic brain injury: Report of an EFNS task force. Eur J Neurol 9:207–219
36. 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
37. Hömberg V (2005) Evidence based medicine in neurological rehabilitation—a critical review. Acta Neurochir Suppl 93:3–14

38. Voss A, von Wild KRH, Prosiegel M (eds) (2000) Qualitätsmanagement in der neurologischen und neurochirurgischen frührehabilitation. W Zuckschwerdt Verlag, Munich
39. Wade DT (1992) Measurement in neurological rehabilitation. Oxford University Press, Oxford
40. Articles of the Association World AMN (2003) www.worldamn.org
41. Prigatano GP (1999) Principles of neuropsychological rehabilitation. Oxford University Press, New York
42. von Wild KRH (ed.) (2005) Re-engineering of the damaged brain and spinal cord. Evidence-based neurorehabilitation. Acta Neurochir (Vienna) [Suppl] 93
43. von Wild KRH (2005) Academia multidisciplinaria neurotraumatologia AMN. Acta Neurochis (Suppl) 93:223–226
44. Gonzalez-Feria L (2000) President's address pp IX-X In: Gonzalez-Feria L, von Wild KRH, Diemath HL (eds) Euroacademia multidisciplinaria neurotraumatologica servicio Canario de Salud, Santa Cruz, Tenerife

Ventricular Enlargement after TBI—Shunt or No Shunt

Hans Tritthart

Summary. Ventricular enlargement is a common sequela of severe traumatic brain injury (TBI) in the post acute and late phase of the trauma. The incidence varies widely in the literature from 30% to 86% of patients examined between 1 and 12 months after trauma. The clear distinction between hydrocephalus and cerebral atrophy as causes of ventricular dilatation has important implications for treatment, but is not always obvious. The syndrome of posttraumatic ventriculomegaly remains a diagnostic and therapeutic challenge. 606 patients (494 men, 112 women) with severe TBI (Glasgow Coma Score of 8 or less) admitted between January 1990 and December 2003 were analyzed. 92 of these patients died of their brain injury in our intensive care unit (ICU). Posttraumatic ventricular dilatation was found in 292 patients (56.8%). Risk factors for ventricular enlargement were age ($P < 0.04$) duration and severity of coma ($P < 0.001$). Many ancillary investigations have been described that can increase the probability of selecting the appropriate patients for a shunt. The reliability and reproduction of these tests are limited. In all our patients CT or MRI provided the anatomical information. The best management is still to adhere strict clinical and magnetic resonance imaging criteria and to rely on a positive cerebrospinal fluid tap test. One or several lumbar punctures with removal of 50 ml cerebrospinal fluid (CSF) was followed by clinical improvement. 24 patients (4.6%) were selected for shunt surgery. Outcome and pitfalls are discussed.

Key words. severe head injury, posttraumatic ventriculomegaly, spinal tap test, shunt

A large number of brain trauma patients develop ventricular enlargement. The incidence varies from 30% to 86% of patients examined up to 12 months after trauma, and it has been proposed as an index of severity of brain damage [1]. The management of ventriculomegaly following severe traumatic brain injury (TBI) still is controversial because it is difficult to determine whether posttraumatic ventricular

Department of Neurosurgery, Medical University Graz, Auenbruggerplatz 29, A-8036 Graz, Austria

dilatation is related to an atrophic process or to a true hydrocephalus. The incidence of postraumatic hydrocephalus (PTH) has been reported as low as 0.7% [2] and as high as 29% [3]. The diagnosis of true hydrocephalus is not always simple. Several variations of the syndrome are seen in the clinical and radiological settings. PTH can present acutely, with progressive coma, the patients can present signs of increased intracranial pressure with disturbance of consciousness and neurological deficits or subacutely, with a history of a gradual decline in daily functioning or in a failure to improve. PTH can present as a normal pressure hydrocephalus (NPH) syndrome with the so called "classical" clinical NPH triade mental deterioration, gait disorder and bladder dysfunction. This "classical" triade of NPH is not classical at all in TBI patients as these patients have so many postraumatic neurological deficits and the classical triade may be misinterpreted.

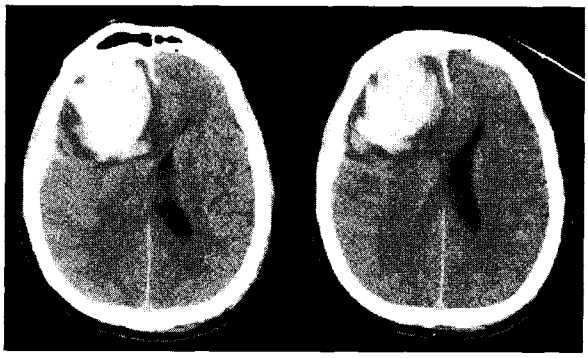
PTH can present as ventriculomegaly by computerized tomography (CT) scanning or magnetic resonance images (MRI) in which the ventricular size is increased, with abnormal dilated cisterns and sulci as seen in cerebral atrophy. Marked widening of the sylvian fissures and cortical sulci may be due to CSF accumulation at the convexity and not to cerebral atrophy. It is very common for cerebral atrophy to occur after head injury, resulting in passive enlargement of the frontal horns and temporal horns and evidence of hippocampal atrophy. This condition has been unfortunately termed hydrocephalus ex vacuo. Alternatively, PTH can present radiologically as an acute obstructive hydrocephalus with presence of periventricular translucency, especially in the frontal horns and obliteration of cerebral sulci (Figs. 1,2).

An increase in ventricular size can be measured subjectively by noting a rounded appearance of the frontal horns, enlargement of temporal horns and third ventricle and can be measured objectively by using the ventricle brain percent ratio (VBR) [4]. This ratio is determined by dividing the ventricle area (determined by measuring the distance between the ventricles at their largest extent) by the intra-cranial area (determined by measuring the distance between the inner table of the skull at its farthest extent) and multiplying by 100. The frontal horn index, or Evans' ratio is the ratio between the widest span of the frontal horns to the maximum width of the brain in the same axial CT section, as a representative of the ventricular size. In this current study, we used the frontal horn index and the ventricular size was considered to be dilated if the frontal horn index equalled or exceeded 0.3. The frontal horn index was calculated using the admission CT and the folllow-up CT scans. In addition, follow-up CT scans were studied for the presence of periventricular translucency.

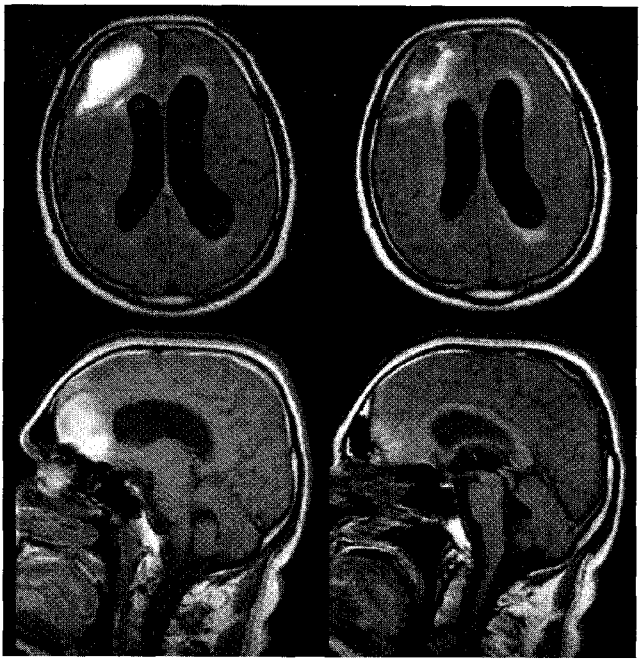
MRI is the best neuroimaging technique for evaluating patients with presumed PTH. It contributes to the differential diagnosis by allowing the assessment of the mean cross-sectional volume of the hippocampal body and the degree of dilatation of the hippocampal fissures. Atrophy of the hippocampus is a marker of atrophy while in PTH the reduction of hippocampal mass is not as evident as seen in atrophy and due to temporal horn dilatation.

1 Patient Population

606 patients (494 men and 112 women) with severe head injury (Glasgow Coma Scale (GCS) score of 8 or less on admission admitted between January 1990 and December



CT 05.22.2001



MRI 07.13.2001

FIG. 1. CT images from a patient with severe TBI with frontal lobal hematoma (05.22.2001). MRI (07.13.2001) with ventriculomegaly and periventricular translucency. The patient was shunted and improved

2003 were eligible for this study. All patients included in this study had CT scan on admission. 92 of these patients died of their brain injury in our unit. This figures look much too good for this clinical population and can be explained by special policies in referring and transferring patients in our hospital. In 544 patients (442 men and 102 women) the intracranial pressure (ICP) was monitored using parenchymal catheters (Codman, Raynham, MA, U.S.A.) up to the end of 1995 and ventricular

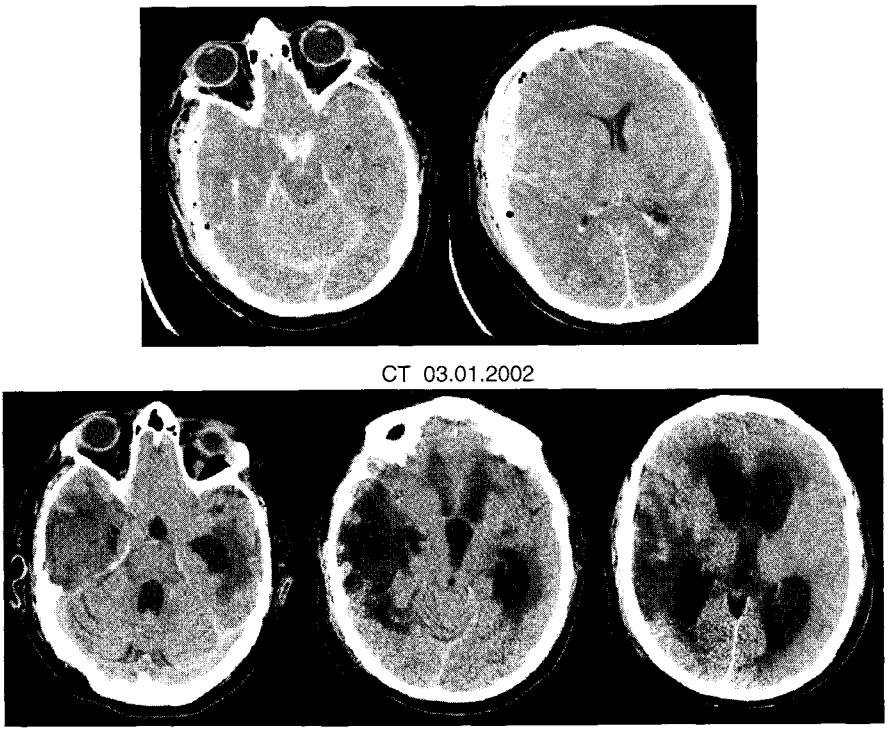


FIG. 2. CT images of a patient with severe TBI and acute hematoma on the right (03.01.2002). CT (04.03.2002) with ventriculomegaly and periventricular translucency. The patient was shunted with minor improvement

catheters (Spiegelberg, Hamburg, Germany) up to now. The effects of prolonged ventricular drainage did not influence significantly the developement of hydrocephalus. We have used many different and sophisticated investigations for selecting the appropriate patients for shunt. Continuous intracranial pressure monitoring commonly shows rises in ICP including 0.5–2/min oscillations (B waves). In normal pressure hydrocephalus occurrence of B waves (i.e. >50 of the ICP recording time) predicts a good response to a shunt [5]. In PTH this was not evident. There are doubts about the value of lumbar CSF infusion test, which measures the resistance to CSF outflow by lumbar or ventricular infusion of artificial CSF [6]. The CSF conductance test (the reciprocal of resistance to CSF outflow) measures CSF reabsorption by constant lumbo-ventricular or ventricular-ventricular CSF perfusion at different CSF pressures [7]. The value of this tests in predicting successful shunt surgery is very high in the hands of some investigators but not in those of others. In view of the controversial predictive value of these tests we decided to manage this problem on strict clinical and CT or MR imaging criteria and rely on a positive cerebrospinal fluid tap test. One or several lumbar punctures with removal of 50 ml CSF was followed by clinical

improvement. This lumbar puncture is not possible in the acute PTH with compressed basal cisterns.

The patients who present acutely with progressive deficits and clear signs of high pressure hydrocephalus benefit from an urgent shunt. The years before this study we started with an external ventricular drainage in these patients and monitored the intracranial pressure (ICP) and finally with clearly elevated ICP these patients were shunted. We found this external drainage was too much and there was no need for it.

Patients who show gradually enlargement of the ventricles can be approached with close observation and CT scans to watch for progression of the ventriculomegaly.

Marmarou et al calculated their patients using the pressure volume index and the resistance for CSF absorption [8]. They found that patients with enlargement of the ventricles and altered CSF dynamics had a poor outcome. Patients with ventriculomegaly and normal CSF dynamic studies suffer from atrophy with no benefit from a shunting procedure.

The outcome following treatment of PTH is variable. 18 patients (78.2%) who underwent a shunting procedure improved, usually one Glascow outcome score (GOS). The timing of treatment has also remained controversial. We found that patients with clinical symptoms of hydrocephalus for less than 3 months have a better prognosis.

The rate of peri- and postsurgical complications ranges between 20% and 40%, but serious complications (death or severe residual deficit) do not exceed 1–2% of shunting patients, mainly patients with substantial comorbidity. Before concluding that poor outcome after surgery is due to the selection of a bad candidat, ineffectiveness of the shunt should be suspected especially in patients in whom the ventricular size did not decrease after a shunt and in those with transient postsurgical improvement. Shunt dysfunction is not uncommon and can be seen in all types of shunts.

The study and others emphasize the importance of subarachnoid hemorrhage (SAH) as a warning sign for the development of PTH. In our study, almost 70% of those patients who developed PTH demonstrated SAH and/or IVH on their admission CT scan.

Alternatives to shunting remain marginal and the crucial problem is still whether to shunt or not to shunt. Ventriculo-peritoneal shunts have become standard treatment although ventriculo-atrial shunts are still a second line option especially in patients with a history of multiple laparotomies. Whatever the type of shunt, the major drawback of all shunting methods is the high rate of shunt related complications resulting in the highest morbidity in neurosurgery. Recent improvements in shunt technologies are aimed at reducing the incidence of technical failure. Technical refinements include antisiphon devices, flow controlled devices and valves with adjustable pressure. In most of the patients with PTH we used conventional hydrostatic valves. The cost effectiveness of such sophisticated technical refinements compared with conventional valves is still under debate and not the problem of this study. The shunt type is not included in the analysis because it does not play a role in the decision to place a shunt. Outcome was better for patients receiving a low than a medium or high pressure shunt, although the differences did not reach statistical significance. In rare cases of aqueductal stenosis third ventriculostomy can be recommended but was done only in one of the study patients.

Of the 24 patients selected for surgery one died of cardiac failure unrelated to the shunt surgery. 23 patients had a complete follow-up of 12 months (mean 11.2 ± 1.9 months). 18 patients (75 %) were shunted during the acute post-TBI period (<100 days post-injury) and 6 patients (25%) were transferred from a neurorehabilitation center.

Two patients had shunt malfunction and the shunt was changed. One patient had a shunt infection and needed an external ventricular drainage and later on a new shunt. The improvement after shunt is not overwhelming, but the patients showed usually one grade higher GOS as seen before shunt and neurorehablitation could be continued. Shunting improved cognitive function in 16 patients (69.5%) within several days, the neurological deficits took longer to resolve. CT scan plays an important role in diagnosis and follow-up, but did not correlate with response to shunting in 11 patients (47.8%). In 12 patients (52.1%) we observed in the follow-up CT scans a reduction in ventricular size and improvement of periventricular translucency.

Possible benefit from ventricular shunting should be carefully weighed against potential complications. Rapid reduction of the ventricular pressure may result in postsurgical hygromas or hematomas. On the basis of our findings, the presence of ventriculomegaly is not an indication of poor prognosis unless it is associated with a negative CSF tap test.

References

1. Blatter DD, Bigler ED, Gale SD, et al (1997) MR-based brain and cerebrospinal fluid measurement after traumatic brain injury: Correlation with neuropsychologic outcome. AJNR Am J Neuroradiol 18:1–10
2. Cardosa E, Galbraith S (1985) Post-traumatic hydrocephalus: A retrospective review. Surg Neurol 23:261–264
3. Hawkins T, Lloyd A, Fletcher G, et al (1976) Ventricular size following head injury: A clinico-radiologic study. Clin Radiol 27:279–289
4. Guyot LL, Michael DB (2000) Post-traumatic hydrocephalus. Neurol Res 22:25–28
5. Symon L, Dorsch NWC (1975) Use of long-term intracranial pressure measurement to assess hydrocephalic patinets prior to shunt surgery. J Neurosurg 42:258–273
6. Katzmann R, Hussey F (1970) A simple constant infusion manometric test for measurement of CSF absorption. I. Rationale and method. Neurology 20:534–544
7. Børgesen SE, Gjerris F, Sørensen SC. (1978) The resistance to cerebrospinal fluid absorption in humans. A method of evaluation by lumbo-ventricular perfusion, with particular reference to normal pressure hydrcephalus. Acta Neurol Scan 57:88–96
8. Marmarou A, Foda MA, Bandoh K, et al (1996) Posttraumatic ventriculomegaly: Hydrocephalus or atrophy? A new approach for diagnosis using CSF dynamics. J Neurosurg 85:1026–1035

Ex vivo Expansion and Neural Differentiation of Bone Marrow-derived Cells under Serum-free Condition

TAKURO MAGAKI, KAORU KURISU, and TAKAHITO OKAZAKI

Up to 20 years ago, it was generally believed that undifferentiated multipotent cells do not exist in adult mammals. But recent studies have revealed that stem cells, which are capable of broad differentiation and self-renewal, exist in various tissues in young and adult mammalian animals. Moreover, these somatic stem cells reportedly possess a differentiation potential to change into functional cells of other organs. Non-neural tissues such as dermis, adipose tissue and bone marrow are thus expected to offer sources of cells for regenerative treatment of severe neurological disorders, including spinal cord injury, traumatic brain injury, Parkinson's disease and stroke.

Bone marrow-derived cells (BMCs) are comprised of hematopoietic stem cells (HSCs) and mesenchymal stem cells (MSCs; also referred as bone marrow stromal cells). HSCs normally differentiate into blood cells, and MSCs produce cells of mesodermal origin. Recent reports have described the ability of BMCs to "trans-differentiate" into neural cells. BMCs are advantageous in the establishment of less invasive harvest procedures and large cell yields. BMCs are also clinically attractive because autologous transplantation can be performed in humans.

BMCs contain heterogeneous groups of cells, and it is suggested by some researchers that BMCs which have potency of neural differentiation may be morphologically and phenotypically different from typical marrow stromal cells. These cells with neural potential are small, oval or spindle-shaped with short processes and no fibronectin immunoreactivity, whereas stromal cells are large, flat and fibronectin-positive. In our experience, these small cells constitute a considerable fraction in primary culture, but percentages rapidly decreased with repeated passage in ordinary fetal bovine serum culture.

Serum-free monolayer culture of rodent BMCs was examined for efficient *ex vivo* expansion of cells that have potential for neural differentiation. Excluding the use of serum prevented the growth of differentiated cells such as fibroblasts. To increase adhesiveness of BMCs to the culture surface under serum-free conditions, coating modulation using extracellular matrix (ECM) was applied.

Bone marrow was harvested from young rats and cultured in serum-free medium containing basic fibroblast growth factor (bFGF) on surface coated with L-ornithine.

Department of Neurosurgery, Graduate School of Biomedical Sciences, Hiroshima University, Hiroshima, Japan

Non-adherent cells were then removed by changing medium. Adherent cells were transferred to dishes coated with ornithine and fibronectin. After transfer to ECM-coated surface, 79.1% of cells attached to the surface. Small, round or spindle shaped cells adhered to the culture surface among large flat cells. Some of these small cells developed short processes. Under serum-free conditions, the small, round or spindle-shaped cells proliferated continuously on the ECM-coated surface. The small cells exhibited particularly robust growth when in contact with large flat cells, and formed clusters. In contrast, large flat cells displayed minimal proliferation under these conditions. The number of BMCs expanded 5.4-fold in 21 days.

Neural stem cell marker nestin was positive on Day 1 and Day 21. Expression of nestin was more intense in small cells than in large flat cells. Processes extending from BMCs also expressed nestin.

The proliferative potency of BMCs under serum-free condition was examined by BrdU immunohistochemistry. The cells labeled by BrdU were observed on Days 1 and 21, and Number of labeled cells did not decrease between these days. This indicates the maintenance of BMC proliferative potency in serum-free culture.

For *in vitro* neural differentiation studies, cells were plated onto ornithine- and fibronectin-coated surface in differentiation medium containing NGF and BDNF. In neural differentiation culture medium, some small cells developed long, thin cellular processes with branches. Some processes attached to the cell body or processes of other cells. Immunohistochemistry revealed that more than half of BMCs expressed neuronal marker β-tubulin III under neural differentiation condition. While many small cells showed intensively positive for neuronal markers, large and flat cells showed weak staining. Processes extending from small cells also expressed the markers. Staining for glial marker GFAP was weaker than for neuronal markers. Expression of nestin was weaker under differentiation conditions.

To evaluate survival and migration of BMCs *in vivo*, cells were transplanted into brain parenchyma of syngenic animals. BMCs under differentiation conditions were labeled prior to transplantation using PKH-26. Undifferentiated BMCs stereotactically inoculated to the subcortex of the hemisphere of syngenic animals. At 3 weeks after transplantation, PKH-26 labeled BMCs visibly survived in the site of transplantation. Numerous transplanted cells remained confined to the injected site, while a small number of cells migrated into the subcortex.

Recent reports have described the ability of BMCs to "trans-differentiate" into neural cells. For neural induction of BMCs, various methods have been reported, such as β-mercaptoethanol, gene transfer and co-culture with neural stem cells, but methods are not yet well-established.

The present study used serum-free culture similar to culture methods for neural stem cells. In ordinary culture of BMCs with fetal bovine serum, large and flat cells proliferate intensely. These large and flat cells require serum for proliferation, and show minimal expansion under serum-free conditions. Serum-free culture thus allows preferential expansion of small cells.

The present study examined a monolayer culture of BMCs under serum-free conditions. The bFGF used for cell expansion in the present study is used in both suspension and monolayer cultures for neural stem cells. The usefulness of bFGF has also been reported for MSC expansion, and bFGF is reportedly useful for maintaining

immature MSCs. In the present study, cultured cells continued to display proliferative activity even on Day 21.

Under serum-free conditions, adhesion activity of cells decreases markedly, and monolayer culture on ordinary treated dishes is difficult. For expansion and differentiation of MSCs, various reports have suggested the usefulness of surface modifications. Ornithine is a non-protein amino acid used as a coating material for neural cell cultures. Coating with this substrate provides strong adhesion of cultured cells to the culture surface. Fibronectin is one of the major adhesive molecules for coating material. The molecule also increases proliferative activity in cultured cells. The combination of ornithine and fibronectin as a coating substrate in serum-free culture of BMCs achieved high adhesiveness for BMCs to the surface.

For the *in vivo* study, cell transplantation demonstrated survival and migration of transplanted BMCs. We are presently extending this investigation to trial transplantation of BMCs into a CNS disorder model.

The present study demonstrated monolayer serum-free culturing of BMCs. The results indicate that BMCs proliferate under serum-free conditions and differentiate into neural lineages. Further investigation is underway to examine long-term cultures, and to elucidate characteristics of the small cells identified in this study.

Head Trauma Related Epilepsy

Tohru Hoshida[1], Kunihiko Kobitsu[1], Shunichi Takeshima[1], Hiroyuki Hashimoto[1], Yeong-Jin Kim[2], Hiroyuki Nakase[2], and Toshisuke Sakaki[2]

Summary

Purpose: Patients or their family sometimes complain that their seizures started after head trauma and believe that their seizures resulted from the head trauma. These epilepsies seem to be trauma associated epilepsy (TAE). Posttraumatic epilepsy (PTE) is recognized that cerebral contusion is clearly shown in the neuroimaging study and epilepsy originates around the contusion. Characteristics of TAE and PTE were studied.

Materials and methods: There were four males in PTE and five males and three females in TAE, whose types of head trauma were cerebral concussion in seven and contusion in one. Ages of seizure onset and epilepsy surgery, duration from head trauma to initial seizure, epilepsy type, and post surgical outcome were compared between these groups.

Results: Average ages of seizure onset were 28 years in PTE and 15 years in TAE. Mean duration from trauma to seizure onset was 12 years in PTE. Seizure started less than a year in six patients in TAE. TAE included left mesial temporal lobe epilepsy in six, and three of six cases demonstrated hippocampal sclerosis. Surgical outcome was excellent in all cases in TAE.

Conclusions: TAE usually occurs within one year after mild head trauma and sometimes shows normal MR finding or hippocampal sclerosis. It is important to determine the exact diagnosis and type of epilepsy after head trauma and good surgical outcome is achieved after epilepsy surgery.

Key words. posttraumatic epilepsy, head injury, temporal lobe epilepsy, focal cortical dysplasia, epilepsy surgery

[1] Department of Neurosurgery, Nara Prefectural Nara Hospital, 1-30-1 Hiramatsu, Nara, and
[2] Department of Neurosurgery, Nara Medical University, Kashihara, Nara 631-0846, Japan

1 Introduction

Posttraumatic epilepsy (PTE) is well known that seizures occur from and near cerebral contusion, and the incidence of seizures is correlated with the severity of head injury [1]. We know some epilepsy patients whose seizures occurred after mild head trauma. Patients or their family often said to us, "the cause of seizures is head trauma", even if head trauma is mild severity. We propose the concept termed "head trauma related epilepsy" "Head trauma related epilepsy" is including two categories. PTE has apparent contusions on MRI and seizures occur from and around the contusion. Trauma associated epilepsy (TAE), whose seizures occurred after head trauma, but no obvious contusion is revealed on MRI. This presentation is aimed to clarify the clinical features and compare the results between PTE and TAE.

2 Subjects and Methods

96 resective surgeries were performed for intractable epilepsy patients. Twelve patients (12.5%) are included in this study. PTE was in 4 males, and TAE was in 8 patients with 5 males and 3 females. Following factors were compared between PTE and TAE; age at head injury, the latency from injury to seizure onset, age at surgery, seizure duration, type of epilepsy, and seizure outcome.

2.1 Illustrative Cases

2.1.1 Case 1

29-year-old man has no risk factors for seizures. Pregnancy and delivery were uneventful and developmental milestones were normal. When he was 4 years of age, he struck his head with no loss of consciousness. His seizure started in the evening on the same day. His seizures became intractable even though optimal three antiepileptic drugs were taking. His seizures consisted of gestural automatism and secondary generalized seizure, and occurred in everyday, maximally more than a hundred per day. He had emergent admissions in several times for status epilepticus. He had a mild head injury, and seemed to have an immediate posttraumatic seizure.

Scalp EEG demonstrated that frequent spikes were shown in right frontal area, Fp2, F4, and F8. Ictal discharges were arising from same areas, Fp2, F4, and F8 (Fig. 1). MRI showed no abnormality. Interictal ECD-SPECT revealed right frontal hypoperfusion. Right frontal lobectomy was performed after subdural grid recording for two weeks, and seizure free for 6 years after surgery. Frontal cortex, where MRI showed no abnormality, was revealed focal cortical dysplasia with bizarre neurons (Fig. 1).

2.1.2 Case 2

Second case is a 42-year-old man. He had no perinatal insults and febrile convulsions. He had a traffic accident at the age of 24. He was admitted for three weeks after mild head injury. A half year later, his first convulsion occurred, and then became intractable. His complex partial seizures consisted of oral and limbs automatisms, neck rotation, and amnesia, and occurred a couple of times in a week. His ictal speech

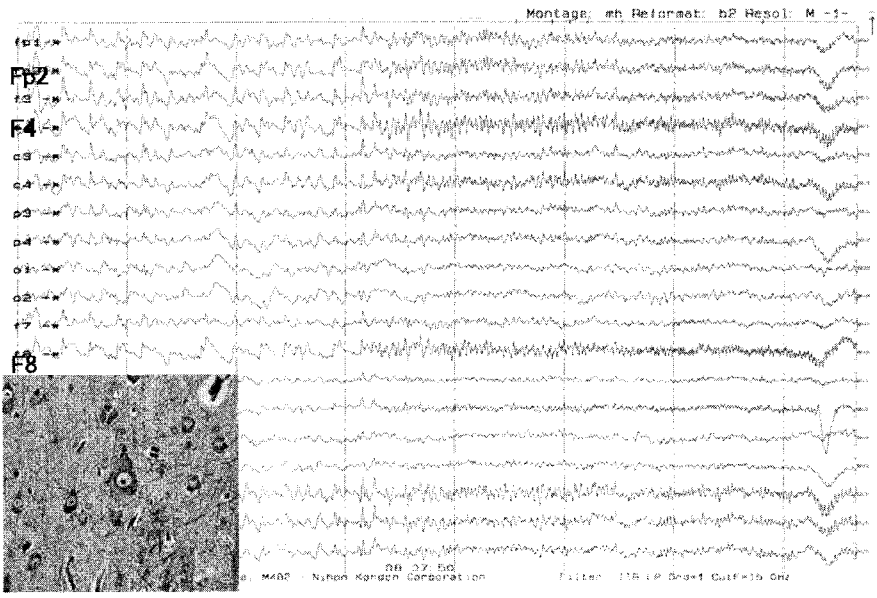


FIG. 1. Ictal scalp EEG in case 1 showed interictal and ictal epileptic discharges were arising from right frontal area. Resected specimen demonstrated focal cortical dysplasia with bizarre neurons

was very interesting and impressive. He repeated, "Help me. Help me. Seizures occurred after head injury. Help me. Help me. Head injury resulted in seizures." He had a mild head injury, and seemed to have a late posttraumatic seizure.

Neuroradiological examinations revealed no abnormality on MRI and no asymmetry in the deoxyglucose PET, interictal and ictal SPECTs, and MR spectroscopy (Fig. 2). Interictal scalp EEG showed independent anterior temporal spikes bilaterally during drowsiness (Fig. 3 left). Left anterior temporal lobe and hippocampus were resected after bilateral temporal subdural grid implantation, and seizure free 33 months after surgery. Resected hippocampus demonstrated gliosis. Postoperative EEG noted right temporal spikes one year after surgery, and no spikes in the temporal area on both sides two years after surgery (Fig. 3 right).

2.1.3 Case 3

Third case is a 38-year-old man. He had a bronchial asthma but no febrile convulsions. A traffic accident had occurred at the age of 17, and loss of consciousness of 2 days. He was admitted for 3 months for operations of an abdominal visceral injury and right elbow fracture. His first convulsion occurred in the same year. Complex partial seizures consisted of dreamy state, automatism and amnesia, and compatible with the semiology of mesial temporal lobe epilepsy (TLE). He had a severe head injury, and seemed to have a late posttraumatic seizure.

Scalp EEG showed that independent interictal spikes were recognized over temporal areas bilaterally. Ictal discharges were clearly arising from left temporal side.

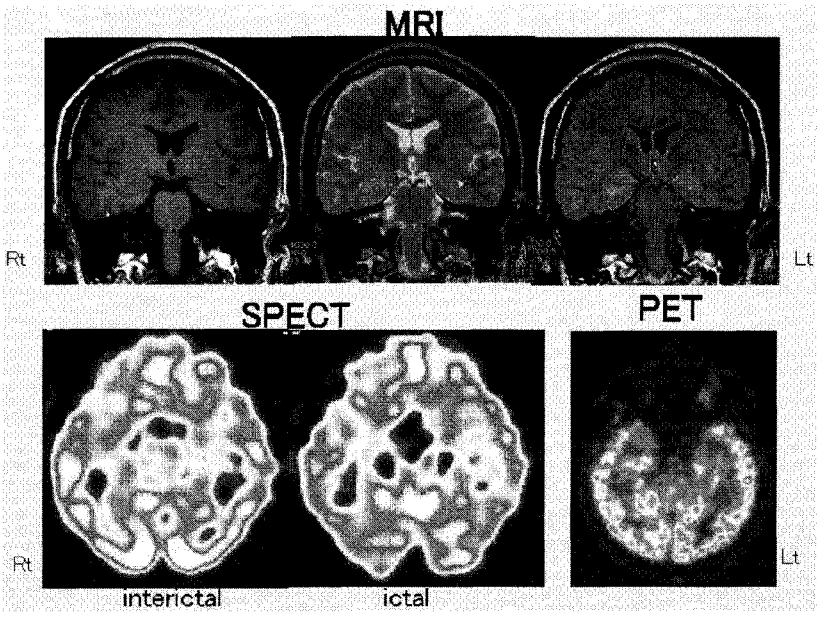


FIG. 2. Neuroimaging studies including MRI, interictal and ictal SPECT, and interictal PET detected no abnormality or asymmetry in case 2

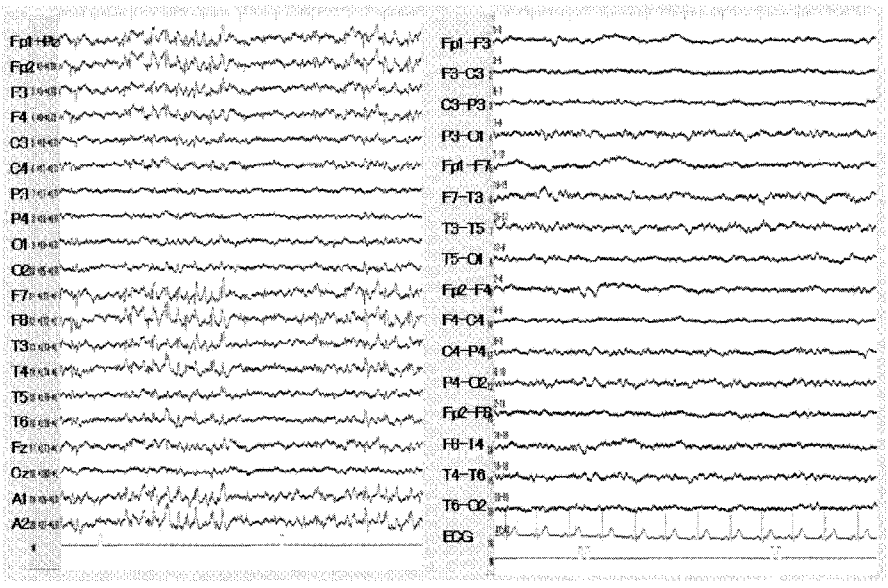


FIG. 3. Preoperative interictal EEG (on the left side) demonstrated independent temporal spikes bilaterally in case 2. Scalp EEG taken two years after surgery (on the right side) showed no spikes at all

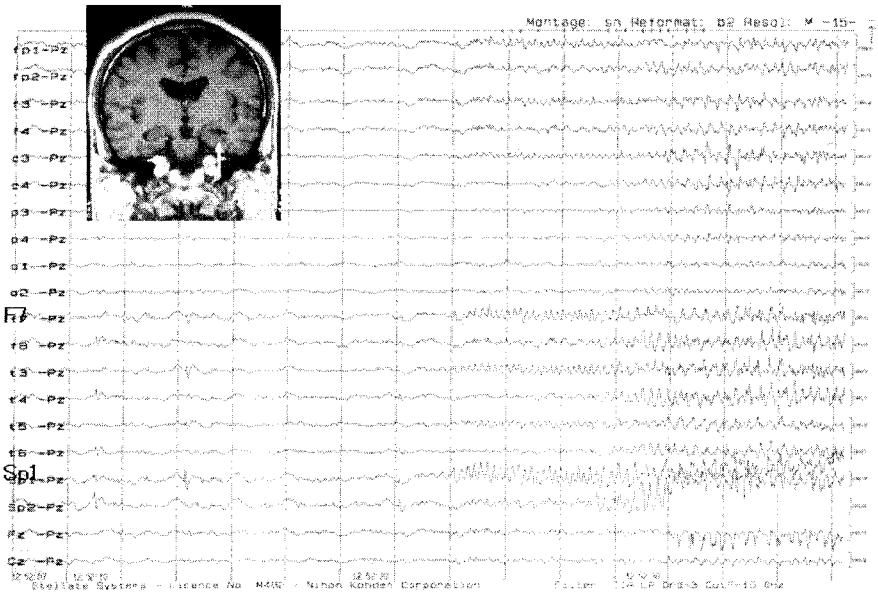


FIG. 4. Scalp EEG in case 3 showed bilateral temporal independent spikes and ictal epileptic discharges were arising from left temporal area. Coronal MRI clearly demonstrated left hippocampal atrophy (*arrow*)

Coronal MRI demonstrated hippocampal atrophy on the left side (Fig. 4). After chronically implanted subdural grid recording, left anterior temporal lobectomy with hippocampectomy was performed, and then seizure free for 6 years. Hippocampal specimen showed typical hippocampal sclerosis.

3 Results

These illustrative three cases are classified into not PTE but TAE. There are four PTE patients in this study. Obvious contusions were recognized in the parietal, temporal, occipital and temporal areas respectively, and then PTE were diagnosed as two temporal, one parietal and one temporooccipital lobe epilepsies. Their outcomes were two in Engel's class 1 and one in class 2 and 4, respectively. In TAE, there were 6 left TLEs, one parietal and one occipital lobe epilepsies. Three of six TLEs had hippocampal sclerosis pathologically. TAE was achieved excellent outcome (all in class 1) after resective surgery. Prognosis after surgery was better in TAE than PTE, but not statistically significant ($p = 0.09$).

Average ages of seizure onset and surgery were 28 years and 38 years of age, and duration from trauma to seizure onset was 12 years in average, ranged from five to 22 years in PTE. On the other hand, average ages of onset and surgery were 15 years and 35 years of age in TAE. Seizure started two years in average after head trauma, ranged from zero to nine years, and less than a year in six patients. Among the clinical fea-

tures, three factors; age at seizure onset, the latency to seizure onset, and age at surgery, were statistically not significant between PTE and TAE.

Mean duration of seizure was longer, 21 years in TAE than 9 years in PTE, and statistically significant ($p = 0.05$). Severity of head trauma was also statistically significant ($p = 0.01$). Seven of eight patients in TAE had antecedent not severe, but mild head injuries, and PTE had severe head injuries in all.

4 Discussions

There are some interesting papers about relationship between head injury and cortical dysplasia. Cohen-Gadol et al [2] reported 22 patients with focal cortical dysplasia of Taylor type. They pointed out that risk factor for epilepsy was trauma in 7 of 22 cases. According to the result of rat experimental model, Lombroso [3] proposed clinical hypothesis. Two children sustained head trauma within six postnatal days and later developmental intractable epilepsy. Neuropathologic analysis revealed an unsuspected microdysgenetic cortex. Early postnatal head injury may induce microdysplastic change over the cortex. As a case 1 suggests us, mild head injury might induce seizures from silent and calm dysplastic cortex when head injury occurred in early immature brain.

The increased risk of seizures after traumatic brain injury (TBI) varies greatly according to the severity of the injury and the time since the injury [1]. As a case 2 shows us, posttraumatic seizure occurs after even if mild head injury is also well known. Jennett et al [4] studied epilepsy after non-missile head injuries. 17% of children younger than five years with "trivial" injuries had an early seizure but only 2% of all patients older than five years including adults and children. Annegers et al [5] reported seizures after head trauma in a population study. Injuries were classified as mild (loss of consciousness or amnesia lasting less than 30 min), moderate (loss of consciousness for 30 min to 24 h or a skull fracture), or severe (loss of consciousness or amnesia for more than 24 h, subdural hematoma, or brain contusion). The frequencies of early and late seizures were 1.0% and 0.2% respectively after mild head injury. Same authors demonstrated later, the standardized incidence ratio was 1.5 after mild, 2.9 after moderate, and 17.0 after severe injuries [1]. According to the study of Lee et al [6], relative risk of deterioration after mild closed-head injury was 0.11%.

These papers suggest us that posttraumatic seizure may occur after mild head injury, but the relationship between new-onset seizures and antecedent head trauma has not been unclear [7]. We propose the term of "trauma associated epilepsy", in which seizure occurred after head trauma, but cerebral contusion is not demonstrated, on the contrast of the term of "posttraumatic epilepsy", in which cerebral contusion is clearly shown by using the neuroimaging study, and seizures occur from and around the contusion.

As case 2 and 3 demonstrate us, TLE may result in TBI, but the mechanism of TLE is poorly understood. McKinney et al [8] demonstrate that recurrent axon collaterals in rat hippocampal slice cultures are newly sprouted by pyramidal cells as a consequence of axonal injury and suggest that this underlies the development of PTE. Whether a single episode of concussive head trauma causes a persistent injury in

neural excitability in the limbic system has not been unequivocally determined. From the results of rodent fluid percussion model, Santhakumar et al [9] demonstrated that a single episode of experimental closed head trauma induces long-term alterations in the hippocampus. Golarai et al [10] confirmed an early and selective cell loss in the hilus of the dentate gyrus and area CA3 of hippocampus, ipsilateral to the impact. The occurrence of selective hippocampal cell death after fluid-percussion injury in rats is consistent with the reported reduction of hippocampal volume bilaterally in humans after TBI and resembling hippocampal sclerosis.

Previous reports have suggested that mesial TLE may result from TBI only in young children (less than five years) [11,12]. Diaz-Arrastia et al [13] identified 23 patients with intractable epilepsy who had TBI after the age of 10 years, preceding the onset of epilepsy. Of the 23 patients, eight had mesial TLE. Two of these patients underwent anterior temporal lobectomies with good postoperative outcome, and hippocampal sclerosis was confirmed pathologically.

5 Conclusions

An association between new-onset seizures and previous head trauma has been unclear. We propose the concept named "head trauma related epilepsy" "Head trauma related epilepsy" is including two categories, that is PTE and TAE. Mild head injury partially contributes to TAE. Shorter duration from injury to seizure onset and longer epilepsy period were demonstrated in TAE than PTE. Occasionally focal cortical dysplasia or hippocampal sclerosis was revealed in TAE. Good prognosis is achieved after precise preoperative examinations and resective surgery in TAE than PTE.

References

1. Annegers JF, Hauser A, Coan SP, et al (1998) A population based study of seizures after traumatic brain injuries. N Eng J Med 338:20–24
2. Cohen-Gadol AA, Özduman K, Bronen RA, et al (2004) Long-term outcome after epilepsy surgery for focal cortical dysplasia. J Neurosurg 101:55–65
3. Lombroso CT (2000) Can early postnatal closed head injury induce cortical dysplasia? Epilepsia 41:245–253
4. Jennett B (1975) Epilepsy after non-missile head injuries. William Heinemann Medical Books, London
5. Annegers JF, Grabow JD, Groover RV, et al (1980) Seizure after head trauma: A population study. Neurology 30:683–689
6. Lee ST, Liu TN, Wong CW, et al (1995) Relative risk of deterioration after mild closed head injury. Acta Neurochir (Wien) 135:136–140
7. Frey LC (2003) Epidemiology of posttraumatic epilepsy: A critical review. Epilepsia 44(Suppl. 10):11–17
8. McKinney RA, Debanne D, Gähwiler BH, et al (1997) Lesion-induced axonal sprouting and hyperexcitability in the hippocampus in vitro: Implications for the genesis of posttraumatic epilepsy. Nat Med 3:990–996
9. Santhakumar V, Ratzliff ADH, Jeng J, et al (2001) Long-term hyperexcitability in the hippocampus after experimental head trauma. Ann Neurol 50:708–717
10. Golarai G, Greenwood AC, Feeney DM, et al (2001) Physiological and structural evidence for hippocampal involvement in persistent seizure susceptibility after traumatic brain injury. J Neurosci 21:8523–8537

11. Mathern GW, Babb TL, Vickrey BG, et al (1994) Traumatic compared to non-traumatic clinical-pathologic associations in temporal lobe epilepsy. Epilepsy Res 19:129–139
12. Marks DA, Kim J, Spencer DD, et al (1995) Seizure localization and pathology following head injury in patients with uncontrolled epilepsy. Neurology 45:2051–2057
13. Diaz-Arrastia R, Agostini MA, Frol AB, et al (2000) Neurophysiologic and neuroradiologic features of intractable epilepsy after traumatic brain injury in adults. Arch Neurol 57:1611–1616

Recent Projects on Neurotrauma in Japan

MINORU SHIGEMORI[1]*

Summary. There are several major projects on neurotrauma in Japan. They include development of Management Guidelines for Severe Traumatic Brain injury (TBI) and Japan Neurotraum Data Bank (JNTDB) by the Japan Society of Neurotraumatology and the Project to establish the Medico-Social Support System for Cognitive and Behavioral Dysfuntion after TBI by the Japan Ministry of Health, Labour and Welfare. The first management Guidelines was published in 2000 based on the result of the Japanes literature review and committee consensus. The revision of the Guidelines is now ongoing and the new version will be published in 2006. The first report on the result of JNTDB was published in 2002 and the second report based on the data with 1002 patients will be released in 2006. The third project reported preliminarey proposal of diagnostic criteria, neuropsychological rehabilitation and social supporting system in 2004 and the final report will be published in 2005. The overview of these projects and the perspectives are reported.

Key words. neurotrauma TBI, guidelines, data bank, cognitive dysfunction

1 Introduction

Traumatic brain injury (TBI) is one of the leading cause of disability and death in young peoples in all over the world. But the mortality and morbidity rates of severe TBI are still remained high [1] in spite of recent advancement of diagnostic and therapeutic modalities. To understand the epidemiology of TBI patients and to standard-

[1] Department of Neurosurgery, Kurume University School of Medicine, 67 Asahi-machi, Kurume 830-0011, Japan

* The members of Guidelines and Neurotrauma Data Bank Committees of the Japan Society of Neurotraumatology and the members of the Committees of the Project on Establishment of Medico-Social Support System for Cognitive and Behavioral Dysfunction after TBI

ize the evaluation and management in acute and subacute stages and to establish an appropriate countermeasures for severe sequelae will be essential to improve the outcome of TBI patients [2–4]. Since the late of 1990, several major projects on neurotrauma have been started in Japan. In this article, the overview of these ongoing projects and the perspectives are reported.

2 Major Projects

Among several neurotrauma projects in Japan, three major projects are now ongoing supported by the official academic societies and government. They include Mangement Guidelines in the acute stage of TBI, Japan Neurotrauma Data Bank (JNTDB) and Project to establish the Medico-Social Support System for Cognitive and Behavioral Dysfunction after TBI. The midterm results of all these projects already published until 2005.

3 Management Guidelines

This project started in 1998 by the Japan Society of Neurotraumatology and the guideline committee has developed the Guidelines for the Management of Severe Head Injury in adults in 2000 [5]. The Guideline was made by the literature review of the Japnaese articles in the last 10 years and committee consensus, and have 8 main topics relating to patients' outcomes including key issues for pediatric and geriatric patients (Table 1). The Guideline is not evidence-based but mixed with the literature-based and consensus-based appropriate for actual medical practice in Japan. But the essence of the Guidelines is similar to other published guidelines from Brain Trauma Foundation (U.S.) in 1995 [6] and European Brain Injury Consortium (EBIC) in 1997 [7].

After development of this Guideline, the committee also started to verify the compliance with this guideline by sending questionnaires to 49 committee members of the Sociey in 2003. The result showed 84% of familiar rate and 95% changed their practice or used for the reference although 57% of them had independent protocol for the managements. Based on the common consensus in the committee that the development of guidelines should be considered as a part of a process and the result of this verification, the update of the Guideline was started in 2003 [3,5]. The revised process is now ongoing with new evidence and new topics including mild and moderate TBI. The new version will be published in 2006.

TABLE 1. Topics of Japanese Guidelines (2000)

1. Neurotrauma care system and neurosurgeons
2. Initial resuscitation for brain protection
3. Primary care from ER to ICU
4. ICU managements
5. Operative indication and timing
6. Management of craniofacial injury
7. New treatment options
8. Management of pediatric and elderly patients

4 Japan Neurotrauma Data Bank (JNTDB)

In 1997, the Japan Society of Neurotraumatology founded JNTDB and started to collect prospective data from major central hospitals managing severe TBI patients with the cooperation of The Japanes Council of Traffic Science. Until then, the details of the epidemiological data have been limited although the Institue for Traffic Accident Research and Data Analysis (ITARDA) under the jurisdiction of the Ministry of Transportation, Construction and the National Police Agency has been publishing annual reports on the results of analysis of roard traffic accidents [2]. During the period of 1998–2000, the enrolled number of patients reached 721 with age ranging from 6 to 94 years whose Glasgow Coma Score of 8 or less during hospitalization and cardiopulmonary arrest on admission (CPAOA). 392 data items relating to mechanisms, type of injury, neurological severity, systemic injury, treatment in acute and subacute stage, follow-up data and outcomes were carefully analyzed. The first results with 721 patients was published in 2002 [8]. The enrolled patients reached over 1,000 in 2001 and the brief essence of the overall results are shown in Figs. 1–4. The characterstic features of severe TBI are two phasic age distribution with high mean age, high incidences of the most serious patients with GCS of 3 or 4, short admission time from injury and major cause of road traffic accident (61%) (Fig. 1). The lesion types of TBI is influenced by the age and mechanism of injury (Fig. 2 and Table 2). The overall mortality rate is high as 50% and this is also significantly influenced by the age (Fig. 3). Early hypoxia and hypotension were encounted in 12 and 21%, respectively, but no significant effects on the patients outcomes. The final result of data analysis will be published in 2006.

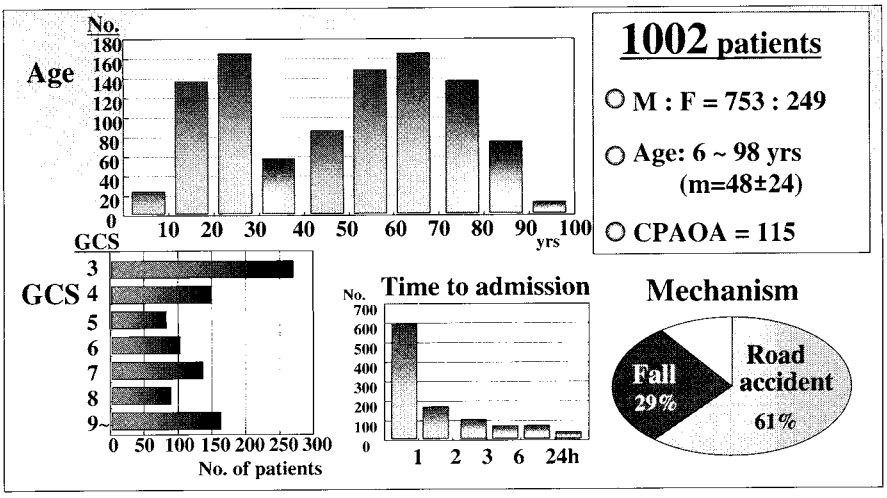


FIG. 1. JNTDB 1998–2001

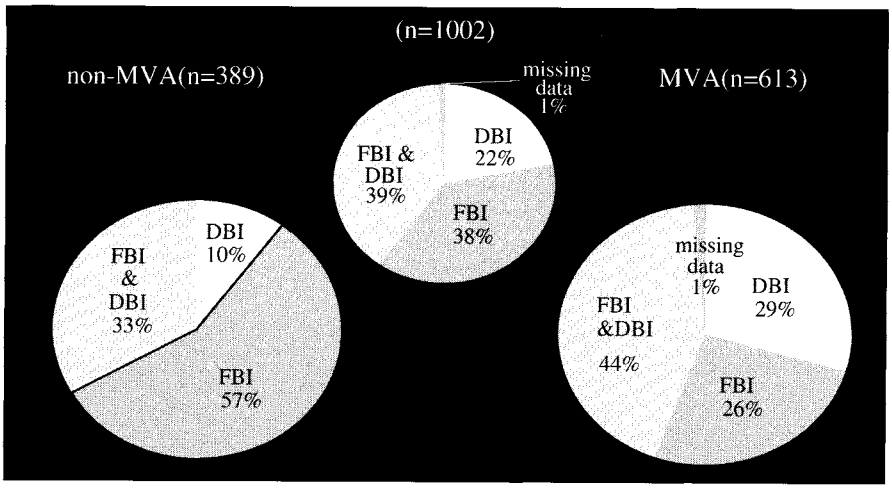


FIG. 2. Type of TBI (DBI and FBI). *FBI*, focal brain injury; *DBI*, diffuse brain injury

Age	Lesion Type(%)						(n : 799)
	D– I	II	III	IV		EM	non-EM
≤ 39	4	104	54	5	167(55.3)	119(39.4)	16(5.3)
40 ≤	2	90	39	6	137(26.2)	265(53.3)	95(20.5)
					304(38.0)	384(48.1)	111(13.9)
					(p<0.00001)		JNTDB 2004

TABLE 2. Age-related characteristics

5 Higher Brain Dysfunction

The Project to Establish the Medico-social Support System for Cognitive and Behavioral Dysfunction after TBI was organized as the model project by the National Center of Rehabilitation under the support of the Japan Ministry of Health, Labour and Welfare in 2001. The background and the aim of this project are to save the patients suffering from severe sequelae after TBI. The local administrations in 13 prefectures

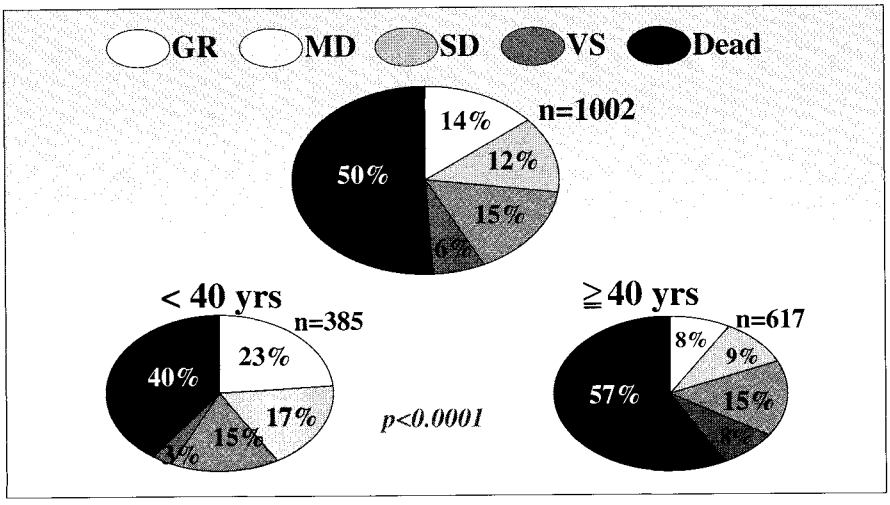


FIG. 3. Outcome of 1,002 patients

TABLE 3. Diagnostic criteria of higher brain dysfunction

- Signs and symptons
  History of organic brain damage, distubances in memory, attention, performance and social behaviour
- Others
  Identification of organic brain lesions by neuroimagings, EEG or other modalities
- Exclusions
  Severe physical handicaps
  Congenital diseases, perinatal damage, developmental disorder, progressive diseases
- Diagnosis
  Fulfill above conditions
  Evaluation after acute phase
  Additional neuropsychological studies by experts

with 15 medical and welfare institutions are participated and 423 patients were registrated during the first 3 years. The result of data analysis of these patients showed common disturbances in memory (91%), attention (83%), performance (77%), followed by interpersonal (59%), dependence (55%), persistence (45%), volition (44%) and affection (44%). The preliminary diagnostic criteria of higher brain dysfunction was then developed (Table 3). The recommended evaluation tests for these higher brain dysfunction were also proposed. Until 2006, the recommended training and rehabilitation measures as well as medico-social support system will be established.

These three major projects are expected to contribute the improvement of the outcomes of patients suffering from TBI in Japan.

References

1. Murry GD, Teasdale GM, Braakman R, et al (1999) The European Brain Injury Consortium survey of head injuries. Acta Neurochi (Wien) 141:223–236

2. Nakamura N, Yamaura A, Shigemori M, et al (2002) Epidemiology, prevension and countermeasures against sever traumatic brain injury in Japan and abroad. Neurol Res 24:45–53
3. Shigemori M, Tokutomi T (1999) Standards and guidelines for the management of severe head injury. Jpn J Neurosurg (Jpn) 8:84–91
4. Shigemori M, Tokutomi T (2002) Result of nationwide survey of the management of severe head injury in Japan. Neurol Res 24:41–44
5. The Japan Society of Neurotraumatology (2000) Guidleines for the management of severe head injury. Neurotrauma (Jpn) 23:1–51
6. Bullock R, Chesnut RM, Clifton G, et al (1995) Guidelines for the management of severe head injury. Brain Trauma Foundation 1–163
7. Maas AIR, Rearden M, Teasdale GM, et al (1997) EBIC guidelines for the management of severe head injury in adults. Acta Neurochi (Wien) 139:286–294
8. The Japan Society of Neurotraumatology (2002) Result of Japan Neurotrauma Data Bank. Neurotrauma (Jpn) 25:117–216

Head Injury in Buenos Aires City: Main Features

PATRICIA S. MARCHIO[1], IGNACIO J. PREVIGLIANO[2], CLAUDIO E. GOLDINI[3], FRANCISCO MURILLO-CABEZAS[4], and ARMANDO BASSO[5]

Summary

Objective: The aim of the study is to present the main features of head injury (HI) epidemiology in a population of Buenos Aires City that represents almost all socioeconomic sectors.

Material and method: Prospective, population based study, approved by the Ethic, Education and Research Committees as part of a neurotrauma program.

Results: HI incidence was 322/100,000 inhabitants, of them mild HI accounted for 93%, moderate HI 4% and severe HI 3%. Average age was greater in women than in men (49 *vs* 38 yo, *P* 0.01). There were differences in the population it it is divided at a cut off age of 40. Relative risk (RR) for any kind of HI was 1.97 (CI 95% 1.77–2.19, $P < 0.01$), RR for motor vehicle (MV) related HI was 2.53 (CI 95% 2.03–3.17, $P < 0.01$) and male drivers had a higher RR (16.76 CI 95% 5.35–52.50, $P < 0.01$) regardless age. Assaults had also a RR 2.11 in people under 40 yo (IC 95% 1.46–3.03, $P < 0.01$) increased in young males. Regarding population over 40 self altitude falls RR was increased (4.35 CI 95% 2.61–4.16, $P < 0.01$) specially in women at any age (RR 3.15 CI 95% 2.57–3.87, $P < 0.01$). Pedestrian accidents were also more common in population over 40 yo (RR 1.84 CI 95% 1.41–2.41 $P < 0.01$). We did not found any other differences concerning remaining trauma mechanisms.

Conclusions: HI incidence in Buenos Aires is similar to other printed series, but moderate and severe HI and mortality rates are below that ones. Motor vehicle accidents are the leading HI cause, especially in the young male population, while self altitude fall and pedestrian accidents are prevalent in women and people over 40 yo.

Key words. traumatic brain injury, head injury, epidemiology, incidence, risk factors

[1] Emergency Room and Intensive Care Unit, [2] Intensive Care Unit, [3] Coordinator Emergency Areas, Hospital General de Agudos J.A. Fernández, Buenos Aires, Argentina, [4] Emergency Room and Intesive Care Unit Head, Hospital Universitario Virgen del Rocío, Sevilla, España and [5] Emerit Proffessor of Neurosurgery, Buenos Aires University, Buenos Aires, Argentina

1 Introduction

Head injury (HI) the so called "silent epidemic" is the leading cause of death and dissability in people above 40 years old. It importance regarding soncieconomic and public health issues has been objet of analysis and lead to a great number of epidemiological publications [1,2,3,4] mainly in the seventies and eighties.

The aim of this study is to find out HI epidemiology in Buenos Aires City through data obtained in a well defined geographical area whose population characteristics represented the complete society picture.

2 Material and Method

2.1 Study Design

Observational, prospective, epidemiological population based. The study was aproved by the Hospital Fernandez's Education and Ethics Committees as part of the Neurotrauma Working Group research program.

2.2 Setting

Hospital Fernandez' programatic area population. This includes 478,700 inhabitants, of them 31,200 live in marginal districts and 2,800 live in "squat houses".

2.3 Data Collection

From October 1st 2000 to September 30th one of the authors (PM) dayly collected the following data: age, sex, time, hour and trauma mechanism, initial Glasgow Coma Scale (GSC) score, risk factors according Italian Guidelines for Mild Head Injury in Adults [5], direct or indirect alcoholic intoxicatin signs, computarized tomography scan classification according Traumatic Coma Data Bank ones [4,6], time spended in the emergency room (ER), destination (discharge, admission to general ward, intensive care unit, derivation to another medical facility, death or run away)

According Italian Guidelines HI severity was divided in mild (GCS 14–15), moderate (GCS 9–13) and severe (GCS 3–8). Data was refereded to programamtic area population so are expressed over 100,000 inhabitants according sex and age. Men/female ratio was established for the complete set and according each age group. Trauma mechanism and severity were analyzed according a pre-established age and sex divition with a cut-off point of 40 years, taking in account the Brain Trauma Foundation Guidelines prognostic factors [7].

2.4 Statistical Analysis

Data collection and analysis was performed using Excel. Chi squarred test was used for discret variables, Odds Ratio (OR) and Realtive Risk (RR) calculation. Two tails Student T Test for median differences was used too. A $P < 0.05$ value was considered significant.

TABLE 1. HI incidence over 100,000 inhabitants according age

	HI total	Mild HI	Moderate HI	Severe HI
Total	322	301	13	9
15–19	321	283	24	14
20–24	868	836	20	12
25–29	630	586	26	18
30–34	499	464	16	19
35–39	356	331	13	13
40–44	325	291	20	13
45–49	301	273	14	14
50–54	277	270	7	0
55–59	186	169	7	10
60–64	152	141	10	0
65–69	179	162	12	4
70–74	336	323	14	0
75–	500	449	13	38

TABLE 2. HI incidence according age, sex and severity

	HI women	HI men	Minor HI women	Minor HI men	Moderate HI women	Moderate HI men	Severe HI women	Severe HI men
Total	124	558	116	520	3	23	4	15
15–19	28	619	14	555	0	49	14	14
20–24	153	1,622	142	1,568	11	30	0	24
25–29	212	1,065	172	1,018	6	48	11	0
30–34	95	965	95	890	0	34	0	41
35–39	59	707	53	658	0	28	6	21
40–44	37	676	30	610	0	45	6	22
45–49	104	545	104	481	0	32	0	32
50–54	150	432	150	417	0	15	0	0
55–59	144	240	144	203	0	15	0	23
60–64	60	276	48	268	12	8	0	0
65–69	133	245	133	204	0	31	0	10
70–74	179	592	171	568	7	24	7	0
75-	454	593	400	545	14	10	14	38

3 Results

In the study period, 58,104 patients consulted to the ER. Of them 1,540 pacients complaint of HI (2.5%), of this population 93% were classified as mild HI, 4% as moderate and 3% as severe.

On Table 1 the incidence over 100,000 inhabitants is shown. Total HI revealed been of 322/100,000 inhabitants, mild HI 300/100,000, moderate HI 13/100,000 and severe HI 9/100,000 respectively. In Fig. 1 are noted three peaks incidence at 20, 40 and 75 years, showing a non gaussian distribution. In Table 2 age and sex incidence is shown. In Table 3 gender relationship accordigng age is exposed. Women were significatively older than men (49 *vs* 37, $P < 0.01$ Student T Test).

TABLE 3. HI ratio between men and women for the complete group and at different ages

	Men/women ratio
Total	4/51
15–19	22/28
20–24	10/58
25–29	5/3
30–34	10/17
35–39	11/92
40–44	18/50
45–49	5/23
50–54	2/87
55–59	1/67
60–64	4/60
65–69	1/85
70–74	3/31
75–	1/31

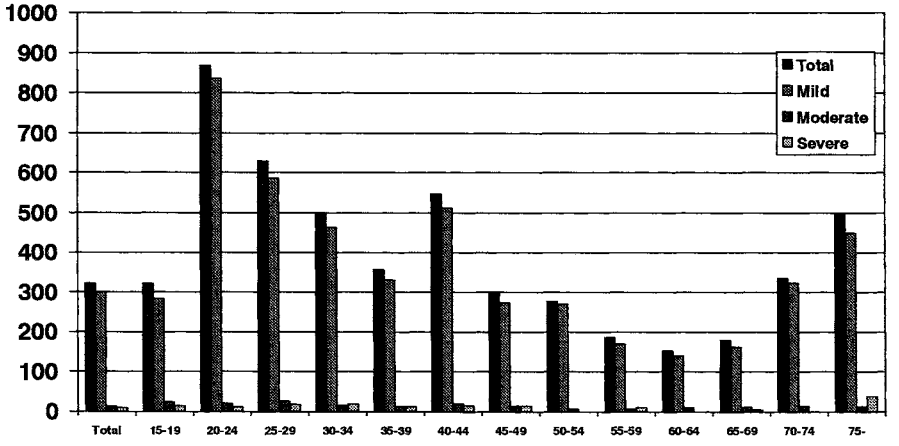


FIG. 1. HI incidence over 100,000 inhabitants. Three peaks identification at 20, 40 and 75 years old population remarks a non gaussian distribution. This is mainly due to mild HI as moderate and severe remains relatively constant

Only 5 HI were due to penetrating lesions and in 261 cases there were associated lesions. Regarding time 30% of HI occurred from 8:00 to 16:00 hours, 39% from 16:01 to 0:00 hours and 31% from 0:01 to 7:59 hours. Risk factors were observed in 59 HI. In 121 patients (8%) HI was related to alcohol intoxication.

In Table 4 absolute and relative numbers according trauma mechanism and sex are revealed.

In Table 5, there is an evident difference in trauma mechanism between victims above and below 40 years old, so each group was analyzed.

TABLE 4. Trauma mechanism for the total group and sex. It is important to note the low incidence of female drivers and the incidence of self-altitude fall in women

Mechanism	Total	%	Men	%	Women	%	*P* value
Traffic	**580**	**37.6**	**419**	**34.4**	**161**	**50**	**<0.01**
Driver	114	7.4	111	10.6	3	0.6	<0.01
Company	104	6.7	45	4.3	59	11.8	<0.01
Motorcycle	124	8	111	10.6	13	2.6	<0.01
Pedrestian	196	12.7	120	11.5	76	15.2	<0.01
Bike	42	2.7	32	3.1	10	2	<0.01
Self-altitude fall	**299**	**19.4**	**119**	**11.4**	**180**	**36**	**<0.01**
Falls	**113**	**7.4**	**77**	**13.1**	**36**	**7.2**	**<0.01**
Seizures	**3**	**0.2**	**3**	**0.3**	**0**	**0**	**0.89**
Head wounds	**86**	**5.6**	**66**	**6.3**	**20**	**4**	**0.42**
Hits	**219**	**14.2**	**170**	**16.3**	**49**	**9.8**	**<0.01**
Violence	**168**	**11**	**144**	**13.8**	**24**	**4.8**	**<0.01**
Unknown	**74**	**4.8**	**44**	**4.2**	**30**	**6**	**<0.01**

TABLE 5. Trauma mechanism according age

Mechanism	<40 years old	%	>40 years old	%	*P* value
Traffic	**370**	**42.3**	**210**	**39.1**	**0.25**
Driver	79	9	25	4.6	<0.01
Company	62	7	52	9.6	0.10
Motorcycle	117	13.3	7	1.3	<0.01
Pedrestian	79	9	117	21	<0.01
Bike	33	3.7	9	1.6	<0.01
Self-altitude fall	**82**	**9.3**	**217**	**40.4**	**<0.01**
Falls	**51**	**5.8**	**62**	**11.5**	**0.01**
Seizures	**3**	**0**	**0**	**0**	**0.59**
Head wounds	**61**	**6.9**	**25**	**4.6**	**0.09**
Hits	**143**	**16.3**	**76**	**13.2**	**0.22**
Violence	**119**	**13.6**	**49**	**8.5**	**<0.01**
Unknown	**26**	**2.9**	**48**	**8.9**	**<0.01**

Statistical analysis revealed that regarding any kind of TBI victims less than 40 years old had a RR of 1.97 ((IC 95%) 1.77–2.19, OR 1.97, $P < 0.01$) greater than the 40yo older as well as a RR of 2 ((IC 95%) 1.79–2.23, OR 2.2, $P < 0.01$) for minor HI, a RR of 1.84 for mild HI ((IC 95%) 1.06–3.20, OR 1.87, $P < 0.02$) and a RR of 1.45 for severe HI ((IC 95%) 0.80–2.63, OR 1.45, P 0.21).

Violence had also a RR of 2.11 ((IC 95%) 1.46–3.03, $P < 0.01$) for younger victims and this ratio augments in young males.

Instead of that self-altitude falls had a RR of 4.35 ((IC 95%) 2.61–4.16, $P < 0.01$) in older victims and a RR of 3.15 ((IC 95%) 2.57–3.87, $P < 0.01$) for women regardless age. Pedestrian victims are also 40yo older with a RR of 1.84 (IC 95% 1.41–2.41, $P < 0.01$).

Regarding CT scans, 219 were performed and their results are shown in Tables 6 and 7. Intracranial hematomas incidence was 1.69%, 0.002 for mild HI. In Table 8 destination after ER discharge is revealed. Only 5.6% needed hospital admission. In Table 9

TABLE 6. Traumatic Coma Data Bank CT classification in absolute numbers and as a percentage of total for each category

TCDB	Mild HI	%	Moderate HI	%	Severe HI	%
1 (Normal)	108	81.8	17	31	4	11.4
2 (Difusse)	20	15.1	13	24	6	17.1
3 (Swelling bilateral)	1	0	5	9.2	5	14.2
4 (Swelling unilateral)	0	0	0	0	0	0
5 (Evacuable mass)	3	2.2	9	16.6	10	28.5
6 (Non evacuable mass)	0	0	10	18.5	10	28.5
Total	132	9.1	54	90	35	83.3

TABLE 7. Intracranial hematoma incidence in absoulte numbers and in percentage of each category

Lesion	Mild	Moderate	Severe	Total
SDH	2 (0.001%)	7 (11.6%)	7 (14.2%)	16 (0.009%)
EDH	1 (0.002%)	3 (5%)	1 (2.3%)	5 (0.003%)
ICH	0	3 (5%)	0	3 (0.001%)
Total	3 (0.002%)	13 (21.6%)	8 (19%)	

SDH, subdural hematoma; EDH, extradural hematoma; ICH, intracerebral hematoma.

TABLE 8. Destination after ER

Destino	Absolute number	%
Discharge	1080	70.1
Derivation	303	19.7
Run away	56	3.6
General ward	51	3.3
ICU	36	2.3
Death on arrival	8	0.5

TABLE 9. Mortality

	Total	Minor	Moderate	Severe
Total	23 (1.56%)	0.00	8 (13.33%)	15 (35.71%)
Males	16 (1.31%)	0.00	6 (11.76%)	10 (31.25%)
Females	7 (2.48%)	0.00	2 (22.22%)	5 (50.00%)

mortality rates are established, 0.5% of patients were death on arrival, 13% of moderate and 36% of severe HI were death.

4 Discussion

To the best of our knowledge this is the first paper that addresses HI epidemiological in Argentina, with a prospective population based design, well-defined groups and a socioeconomic environment that represents today's most of Argentinean society. This is one of our paper's strong points.

One limitation of our study could be the fact that in weekly working hours area study population rises to 800,000 inhabitants, but almost 70% of HI occurred beyond that hours.

According Torner y Shootman [8,9] one source of error in epidemiological HI trials is under registration. Buenos Aires City Government health plan established that victims of all accidents occurring in the streets or in house are sent to the reference hospital by means of the Emergency Medical System (SAME), so under registration is lack to occur.

We decided to classified patients according GCS because it is the most commonly used scale, with less interobserver variances. Although ICH 9 or 10 are the most used classifications in epidemiological studies, they are retrospectives and hospital based, fact that could explain differences in mild, moderate and severe HI rates.

HI incidence in our area (322/100,000 inhabitants) is in the upper range of published studies (90–400/100,000) [4]. In USA [2,4] as well as in Spain [24] rate is 200/100,000. Of them 500,000 victims suffered severe HI, with 50,000 deaths on arrival. Studies in England, Scotland and Wales, showed rates between 270–313/100,000 [4]. In France, two trials showed a 281/100,000 rate [6,10] with different trauma mechanism (less traffic accidents and greater self-altitude falls). In Italy, in 1998, rate was 314/100,000 [11], similar to Johannesburg (South Africa) 316 HI per 100,000 [12], but different than Samoa, in which Wallace [13], found in 1993 a less incidence (165/100,000). Other recent retrospective studies [1,8,10,11,14], also describes similar rates with variations on trauma mechanism.

A particular note of our study is the age difference between male and females that could be attributed to women longer life expectancy. Male/female ratio is in the published range [2,3,6,7,10–12,14–18] with coincident age variations.

Due to traffic related accidents our results are more coincident with papers published in the 70's. Violence is the third leading cause as well as in almost all the publications.

Regarding mortality, Torner y Shootman highlights that most of death occurred previous to hospital admission. According to them [9] mild HI had a 1% mortality, moderate HI a 18% and severe HI a 48%. Our results showed lower values probably due to the fact that our study is prospective, with well-defined groups and in a different chronological time (90's *vs* 70 and 80's). In Table 10 we compared our results with the classic ones.

In summary in this Buenos Aires City population, and probably in Argentina, we found an important HI incidence, with severe and moderate HI incidence below the published in other series. Traffic accidents are the leading cause of trauma, affecting

TABLE 10. HI incidence, mortality and severty rates in population based studies

Population	Year	Méthod	Type	Rate 10^5	Mortality (%)	Minor (%)	Moderate (%)	Severe (%)
Olmstead [19]	65–74	Retrosp.	Pob.	193	11	63	29	7
San Diego [20]	78	Retrosp.	Pob.	295	7	91	91	9
San Diego [21]	81	Retrosp.	Pob.	180	14	82	9	9
Charlottesville [22]	78	Retrosp.	Hosp.	208	7	49	26	25
Chicago (blacks) [23]	79–80	Retrosp.	Hosp.	403	8	86	9	5
Aquitaine [8]	86	Prosp.	Pob.	134	8	80	11	9
Johanesburgo [17]	86–87	Prosp.	Hosp.	91	22	88	7	5
Cantabria [13]	88	Retrosp.	Pob.	316	25	88	8	5
Buenos Aires	03	Prosp.	Pob.	322	1.34	93	4	3

Modify from Torner [9].

Prosp., prospective; Retrosp., retrospective; Pob., population based; Hosp., hospital population based.

mainly young males. Self-altitude falls and pedestrian accidents are the ones in females and older victims. Mortality rates are in the range actually admitted as normal.

We think that these data could signify a value information for public health policies as well as a starting point for further investigations.

References

1. Andersson EH, Bjorklund R, Emanuelson I, et al (2003) Epidemiology of traumatic brain injury: a population based study in western Sweden. Acta Neurol Scand 107:256–259
2. Finfer SR, Cohen J (2001) Severe traumatic brain injury. Resuscitation 48:77–90
3. Gilli Miner M, Murillo Cabezas F, Perea Milla E (1998) Epidemiología y prevención de los traumatismos. In: Martínez Navarro F, Antó JM, Castellanos PL, et al (eds) Salud Pública. McGraw-Hill Interamerica, Madrid, pp 000–000
4. Jennett B, Mac Millan R (1981) Epidemiology of head injury. Brit Med J 282:101–104
5. The Study Group on Head Injury of the Italian Society for Neurosurgery (1996) Guidelines for minor head injured patients' management in adult age. J Neurosurg Sci 40:11–15
6. Marshall L, Marshall S, Klauber M, et al (1991) A new classification of head injury based on computerized tomography. J Neurosurg 75(S):14
7. Brain Trauma Foundation (2000) Management and prognosis of severe traumatic brain injury. Part II: Early indicators of of prognosis in severe traumatic brain injury. Age. Brain Trauma Foundation, pp 27–38
8. Torner JC, Shootman M (1989) Epidemiology of closed head injury. In: Becker DP, Gudeman S (eds) Textbook of head injury. W B Saunders Company, Philadelphia, PA
9. Torner JC, Shootman M (1996) Epidemiology of closed head injury. In: Rizzo M, Tranel D (eds) Head injury and the postconcussive syndrome. Churchill Livingston, New York, pp 19–43
10. Tiret L, Haysherr E, Thicoipe M, et al (1990) Epidemiology of head trauma in Aquitaine (France), 1986: A community-based study of hospital admissions and deaths. Int J Epidemiol 19:133–140

11. Servadei F, Verlicchi A, Soldano F, et al (2002) Descriptive Epidemiology of head injury in Romagna and Trentino. Comparison between two geographically different italian regions. Neuroepidemiology 21:297–304
12. Nell V, Brown DSO (1991) Epidemiology of traumatic brain injury in Johannesburg II. Morbidity, mortality and etiology. Soc Sci Med 33:289–296
13. Wallace GL (1993) Stroke and traumatic brain injury in Amerika Samoa. Hawaii Med J 52:234–250
14. Meerhoff SR, de Kruijk JR, Rutten J, et al (2000) Incidence of traumatic head or brain injuries in catchment area of academic hospital maastricht in 1997. Ned Tijdschr Geneeskd 144:1915–1918. (Abstract)
15. Lopez Bastida J, Serrano Aguilar P, Duque Gonzalez B (2004) The economic costs of traffic accidents in Spain. J Trauma 56:883–889
16. Masson F, Thicoipe M, Aye P, et al (2001) Aquitaine group for severe brain injuries study. Epidemiology of severe brain injuries: A prospective population-based study. J Trauma 51:481–489
17. Raja IA, Vohra AH, Ahmed M (2001) Neurotrauma in Pakistan. World J Surg 25:1230–1237
18. Thornhill S, Teasdale GM, Murray GD, et al (2000) Disability in young people and adults one year after head injury: prospective cohort study. BMJ 320:1631–1635
19. Annegers JF, Grabow JD, Kurland LT, et al (1980) The incidence causes and secular trends of head trauma in Olmstead County, Minnesota, 1935–1974. Neurology 30:912–919
20. Klauber MR, Barret Connor E, Marshall LF, et al (1981) The epidemiology of head injury. A prospective study of an entire community: San Diego, California, 1978. Am J Epidemiol 113:500–509
21. Klauber MR, Marshall LF, Barret Connor E, et al (1981) Prospective study of patients hospitalized with head injury in San Diego County, 1978. Neurosurgery 9:236–241
22. Jagger J, Levine J, Jane J, et al (1984) Epidemiologic features of head injury in a predominant rural population. J Trauma 24:40–44
23. Krauss JF, Black MA, Hessol N, et al (1984) The incidence of acute brain injury and serious impairement in a defined population. Am J Epidemiol 119:186–201
24. Vazquez Barrero A, Vazquez Barrero JL, Austin O, et al (1992) The epidemiology of head trauma in Cantabria. Eur J Epidemiol 832–837

Can Mild Head Injury Affect the Quality of Life by Neuropsychological Disturbances?

Alexandru Vlad Ciurea[1], Ligia Tataranu[1], and Virginia Rotarescu[2]

Summary. We take into account the patients with MHI admitted to the hospital between January 2000 and December 2003. A group of 170 cases (96 children and 74 adults) underwent neuropsychological testing associated to the neurosurgical evaluation and was followed for a period of 12 months. The most common causes of MHI were traffic accidents and assaults for adults and falls for children. Admitted adults had CT scan alterations (25.6%) and 8.1% required neurosurgical interventions. The proportion of children with detectable CT scan abnormalities was smaller (19.7%) and surgery was necessary in only 5.2%. Post-concussion syndrome was observed in 27% cases of children and 18.9% of adults. Neuropsychological tests were performed to evaluate neuropsychological, emotional, psychosocial and behavioural impairments. The study has shown that behavioural disturbances were observed after MHI mainly in adults, and cognitive dysfunctions mainly in children (especially deficits in information processing speed, memory, and attention). Disability was less severe and recovery was better in adults. The neurosurgeon should be aware of the possibility for neuropsychological deficits after mild head injury and he should refer appropriate patients to a neurologist or psychiatrist for further evaluation and/or therapy.

Key words. mild head injury, post-concussion syndrome, cognitive dysfunctions, behavioural disturbances

1 Clinical Material and Methods

1.1 Research Design

This research is a longitudinal and transversal study on admitted patients who suffered a MHI. The criteria for including the patients in the study are GCS of 14–15 and

[1] Neurosurgical Clinic, [2] Neuropsychological Laboratory, "Bagdasar—Arseni" Clinical Hospital, "C. Davila" Medical School, Sos. Berceni, Bucharest, Romania

Correspondence: Ligia Tataranu, Neurosurgical Clinic, "Bagdasar—Arseni" Clinical Hospital, "C. Davila" Medical School, Sos. Berceni 10-12, 041914 Bucharest, Romania

no other associate conditions. The study is revealing the changes occurred in 12 months after MHI with individual visits at 3 months. The final goal is to make comparison of these changes, the outcomes and the MHI consequences in both adults and children in order to evaluate the quality of life.

1.1.1 Methods

- "armed" clinical observation—with a wide range of strategies, techniques and instruments in order to establish the attitudes, the behaviour and the personality, with all the mechanisms used by the patient;
- the "ex post facto cause-effect experiment" cantered on establishing a functional relationship between MHI values (the independent variable) and the changes revealed in patients condition;
- standardized and half-standardized and free talking, according to situation's peculiarities and to subject's psychological characteristics;
- psychological inquiry based on conducted clinical interview;
- psychometric methods based on psychological tests.

1.1.2 Instruments

- Wechsler complete tests battery—for adults "Wechsler Adult Intelligence Scale" (WAIS) and for children "Wechsler Intelligence Scale Children" (WISC)—have ten specifics subtests, which describe different cognitive functions. Personal scores are converted in standardized scores, according to age, in order to find out intelligence quotient (IQ)—verbal, non-verbal and total IQ—and allow comparison between the patients and same age healthy subjects. The mean and the standard deviation of personal results were used for to make a personal deficits picture after MHI, like the pathological significant. The calculated quotient of deterioration (QD) permits the comparison of individual with himself before traumatism (with the previous patient's performances).
- "Galveston Orientation and Amnesia Test" (GOAT) emphasizes the space-time orientation and the presence of post-traumatic amnesia.
- "Wechsler Memory Scale" (WMS) for adults is a complete battery to explore different types of memory in order to identify the deficits; the age-related standardization allows the quotient of memory (QM) calculation.
- The "Rey Auditory Verbal Learning Test" emphasizes the volume of attention and memory according to age, work speed, the fatigability curve and a wide range of behavioural and personality characteristics.
- "Prague Distributive Attention Test" allows standardized interpretation of performances, work rhythm and fatigability curve according to age.
- At the mood level assessment—"Depression inventory for children", developed by M.Kovacs and "Cattell Anxiety Questionnaire" for adults.
- For personality in adults—"The Schmiescheck Questionnaires" for accentuated tendencies and "Woodoorth Personal Data Sheet".
- The parents completed "The Social-Affective Scale" for children.

1.2 Neuropsychological Perspective

The study was conducted between January 2000 and December 2003. The patients were distributed in two groups according to age: the first group with 96 children, ages 5–15 years, and the second group with 74 adults between 16–60 years. Both groups were selected according to EPSEM principle (Equal Probability of Selection Method), based on following criteria: GCS score between 14–15 and no associate conditions, in order to eliminate the combined effects. The mean of the age in children was 10.46 (SD = 3.35) and in adults was 33.46 (SD = 11.14); the distribution appeared like normal. The distribution by sex was preponderantly for male (70.8% in children and 64.9% in adults).

The causes of the injury were: falls (children—60.4%; adults—13.5%), traffic accidents (children—37.5%; adults—37.8%), assaults (children—2.1%; adults—37.8%) and accidents at work (adults—10.8%). People living in cities were more affected than people from villages. Most adults (29.7%) have just a basic form of education.

From admitted adults, 25.6% (19 cases) had CT scan alterations and 8.1% (6 cases) required neurosurgical interventions. The proportion of children with detectable CT scan abnormalities was smaller (19.7%—19 cases) and surgery was necessary in only 5.2% (5 cases). Post-concussion syndrome was observed in 27% cases of children (26 cases) and 18.9% of adults (14 cases).

1.3 Collecting Data

The first contact with patients was established 24 h after admission, after medical check-up was done by the neurosurgeon, in order to offer data for a selection base. Initially, the GOAT was completed with all patients over 7 years (the normal score is between 76 to 100), in order to emphasize the space-time orientation and amnesia. The mean score was for children 89, 05 (SD 19, 31) and for adults 90, 65(SD 14, 53). Initially the patients were assessed after the MHI in multiple sessions and they were following up and reassessed at 3, 6, 9 and 12 months. Structured interviews with the patients and their families were also completed for identifying the personal history and changes in the scholar, professional and familial functioning. Our attention was focused on detection of hypothetic dissimulations, due to desire to obtain some secondary gains.

1.4 Statistical Analysis

The collected data were descriptive and inferential processed with SPSS 10.0 (Statistical Package for Social Sciences). The first step was describing the distribution, main tendencies, variability and correlations. The second step, using the nonparametric inferential, was to estimate the probability of the aleatory deviations.

2 Results

The neuropsychological recovery is not uniform among a group of patients, because each individual has his own recovery rhythm. Level of consciousness decreased immediately after the MHI, that is, a transient alteration of consciousness including partial

or complete loss of consciousness (LOC). Amnesia could appear, including the time precedent, during, and subsequent to the injury. In both samples, the subjects presented preponderantly dizziness (41.7% in children and 35.1% in adults). LOC for minutes is more specific in children and the amnesia is more specific in adults. In the next hours after MHI, the recorded deficits are not specific, but they concern efficiency of information processing, execution and mental processes integration.

2.1 Cognitive Dysfunctions

2.1.1 Attention

Focused attention and short-term memory were studied using the "digit span" subtest from WAIS/WISC (normal standard score is 10). Initially, a slight deficit (mean score std. = 9, 1) was identified in children (r 0.244, $P < 0.01$), but this deficit is recovered in the future. After 3 months the standard mean score is 9.2, at 6 months is 9.4 and 9.6 at 12 months. These deficits are obvious in developing an activity, in attention involvement in simple situations and in diminished the mental activity (chi square 0.000, $P < 0.01$). In adults there are not statistically significant correlations.

The distributive attention was studied with "digit symbol" subtest from WAIS/WISC (the normal standard score is 10). The initial results show the mean score less than in focused attention (mean std. = 8, 5). The outcome is variable with higher scores at 3 months (mean std. = 9.3), poorer scores at 6 months (mean std. = 9.1) and upper at 12 months (mean std. = 9.4). Usually, the divided attention is more disturbed than focused attention, because there are some difficulties in maintaining and switching attention. The consequences are difficulties in performing efficient complex tasks, involving multiple simultaneous decisions, although the patients are capable to perform each simple task apart. The bigger the age, the more disturbed is the divided attention, so the smaller children have better performances. There are no statistically significant differences for adults.

The attention volume was estimated using the results of first trial from "Auditory Verbal Learning Test". The results were compared on a percentile scale, according to patient's age (the normal score is 100%; the slight deficit is flanked by 80–99%; the medium deficit is between 40–79% and sever deficit is less than 39%). Initially, children show a decrease of attention volume (mean score = 72%). This, increase at 79% after 3 months and after 6 months the score develop into stable at mean score 87%. There are no statistically significant differences for adults. Girls have worse performances (61%, 74%, and 79%) than boys (77%, 81%, and 90%).

2.1.2 Information Processing

Information processing capacity is inferior because of deficits of adjustment and task integration (low attention volume) as a consequence of focusing efforts ("digit span"), difficulties in ocular-motor coordination ("digit symbols"), emotional distractibility and increased reactivity, low motivation and little interest along with increased tiredness. During the first few days after MHI, increased fatigability is present in both children and adults and is positively associated with orientation and event remind capacity (GOAT) (chi square 0.000, $P < 0.01$). After 12 months, in children the fatigability is absent. In adults, this parameter is increased.

2.1.3 Memory

Memory in children presents deficits both for information storage and for information access. These deficits are present, for audible range, into medium and long-term memory. The memory volume was estimated with "Auditory Verbal Learning Test" and the results were compared on a percentile scale, according to the age (the normal volume score is 100%). The initial examination shows, in our study, a medium deficit of memory volume (mean = 79%). This, increases after 3 months to 86% and is stable in follow up. There is a negative correlation with age (rho −0.283, $P < 0.01$), with lower performances in older childhood (chi square 0.000, $P < 0.05$). As a consequence, the memory volume in 14–15 years is 72% at the first examination and increasing to 83% after 3 months, decreased to 81% at 6 months and, after 12 months, is 82%. For patients between 11–13 years, mean memory volume is steady (80%). There are no statistically significant differences for adults.

The deficits of visual memory are influenced by GCS score in adults (rho 0.363, $P < 0.01$). The "visual retention" subtest from "Wechsler Memory Scale" was used: subjects watched 3 drawings, each for 10 s, and then reproduced this drawn by the memory. The personal results are conversed directly in percentiles (the normal score is between 80% and 100%). In children, the mean standard score was 58% (GCS = 14) and 70% (GCS = 15). For adults, the mean standard score was 53% (GCS = 14) and 69% (GCS = 15). The adults recover better than children after 12 months. There is no statistical significance in children. The age is in positive relationship with visual memory in children (rho 0.340, $P < 0.01$) and negative relationships in adults (rho −0.454, $P < 0.01$), which suggests that extreme ages have visual memory with low performance. The lowest performances were described in people between 46 and 60 years (mean initial score 34% increase after 12 months at 54%).

All these results lead to the conclusion that, in children, cognitive functions are disturbed by MHI because the brain is functioning in global manner. Consecutively, the selection, the organization and the storage of information can be unsuccessful and the patient can ignore important details that affect the accuracy of memory. The patients have difficulties in acquiring the new information and their habits so; in consequence, they are disturbed in daily routine.

2.1.4 Integrative and Conceptual Thinking

Integrative and conceptual thinking was estimated with "objects assembly" subtest from WISC. There are some deficits in making spontaneous correlations. In our study, these deficits are present in 22.7% of the children, with medium disability (13.6%) and severe disability (9.1%). In children there are positive associations between "objects assembly" and orientation at the accident's moment ($r = 288$, $P < 0.01$), which suggests that loss of consciousness for few minutes leads to medium or severe deficits; there are negative associations between "objects assembly" and fatigability (rho −0.420, $P < 0.01$). In other words, severe deficit is associated with low fatigability, which reinforces the relation between deficit and loss of consciousness (chi square 0.000, $P < 0.01$). There are no statistically significant differences for adults.

Quality of conceptual thinking is altered. The patient becomes unable to correctly interpret information—generalize or concretize. The verbal expression of his thoughts is not concise or accurate; the ideas can be in manners spoke of imprecise

with difficulties to find the appropriate words and the discourse can be dominated by pauses. Nonverbal interpretation beside a perceptive organization with anticipations towards rapidly selection and a reason by decision is deficiently and cause the decreased in flexibility and adaptation at unfamiliar.

2.2 Structures and Personality Characteristics of the Samples

The "Social-Affective Scale" was used for children's premorbid assessment and to emphasize their outcome and the adults were assessed with the "Woodoorth Personal Data Sheet" and "The Schmiescheck Questionnaires" for accentuated tendencies. At the admission's time, 44% of children were dependent type, 31% dominant type, 13% were normal and 12% rebel type. The profile of adults group is characterised by disharmonic structure: hyperperseverence, cyclothymic and affective lability; the vulnerability interested in stress is done by emotivity, hysteroid and epileptoid tendencies accentuated at the neurotics level.

2.3 Mood and Behaviour Changes

"Kovacs children's depression rating scale" and the "Cattell Anxiety Questionnaire" for adults were used. At admission, 50% of children were without depression, 28% with mild depression and 22% with moderate depression. For the adults, the anxiety was severe in 23%, medium in 44% and normal in 29%. In children, the dominant type, even with a slight affection of the consciousness as a consequence of the trauma (rho 0.353, $P < 0.01$) is predisposed to loss by deterioration (rho −0.388 $P < 0.01$) while the dependent type isn't affected by this kind of loss even if one suffers the loss of consciousness few minutes. A normal mood excludes loss of consciousness in MHI, as the orientation at the time of the accident is positively related to depression (rho 0.280, $P < 0.01$). In our study, loss of consciousness for seconds is correlated with moderate depression for girls (within 14–15 years old) and with mild depression for boys (within 11–13 years old) (rho 0.376, $P < 0.01$). At 12 months after MHI, medium depression is observed at 38% of the children within 8–10 years old and 38% at those within 14–15 years old. For adults, severe depression is found only in the group of age within 36–45 years old while patients of other age (mainly those of 26–35 years old) present medium depression. Medium depression at 12 months after MHI is responsible for loss of patients' abilities, because it significantly correlates (rho 0.368, $P < 0.01$) with quotient of deterioration (QD), estimation based on standard scores at WAIS. QD allows comparison of patients' abilities with the ones they had before the accident and explains the personal deficits.

In children, the symptoms by the time they hospitalise are correlated with WISC "Image completion subtest" (rho −0.450, $P < 0.01$) and with GOAT score (rho 0.265, $P < 0.01$) in a dependence relationship. "Image completion" is influenced by the orientation at the time of accident on which the symptoms depend. There are no statistically significant correlations between the symptoms and premorbid structures. In evolution, the changes at these levels are influenced by the GCS score (rho 0.276, $P < 0.01$). The brain injury caused by the traumatism is suggested through these results so that, at a 14 points GCS score and with amnesia, the sever deficit at this test it is recorded for 9% of the studied children. The normal framing of the results has been

obtained for 75% of the patients, 7% scored superior and 9% scored a medium deficit. While observing during one year after the MHI, the symptoms were expressed or not, depending of the endured requires. The headache was most frequent, sometimes associated with tiredness or/and dizziness even after 12 months after suffering the accident. In our survey, 4 children (4.2%) described grand-mal seizures after 3 months and 2 children (2.1%)—after one year—were still describing them. There were no mixtures of stressfully events in the children' social-familial environment during this study.

On adults, the symptoms correlate with the initial anxiety, that keeps them up (at 3 months rho 0.498, $P < 0.01$; at 6 months rho 0.351, $P < 0.01$; at 12 months rho 0.340, $P < 0.01$) and the presence of the symptoms keeps up the anxiety one year after the traumatism (correlation at 3 months rho 0.494, $P < 0.01$; at 6 months rho 0.330, $P < 0.005$; at 12 months rho 0.313, $P < 0.05$). The headaches, the dizziness, slight deficits, anosmia and tiredness are the persistent ones. Advancing, the symptoms are expressed in connection with anxiety. Most times, the symptoms are considerated as a new state to which they must adapt, therefore spontaneous symptoms expression is frequently avoided in order not to be interpreted as wails, which could increase coping efforts.

Psychotherapy is an effective intervention starting with the patient's hospitalisation. The binomial comparison test of the obtained results through psychotherapy confirms the affirmations stated above and expresses the significant difference between the two groups. Trough psychotherapy ascertain deficits are being corrected and the personal performances improves, which leads to a better adaptation on daily solicitations, thus improving life quality of the MHI affected person. 74% of good results were obtained in children with falls (for chi square 0.044 and $P < 0.05$) and 78% in adults with traffic accidents (for chi square 0.008 and $P < 0.05$).

3 Discussions

The quality of life is an evaluative concept, resulted by comparing the conditions of life and the human life's activities with the human necessities, values and aspirations. It refers to the global evaluation of life, as well as to the evaluation of the different conditions or spheres of life. The quality of life represents a different description to the concept of happiness (subjective state resulted from living one's own life) were the interest is focused mainly on determining the objective factors responsible for the life's quality variation and on the strategies of action in order to increase it.

Postinjury behaviour problems in patients with MHI may be associated with preinjury difficulties [1]. The following behaviours can be associated with MHI: hyperactivity, sleep disturbances, appetite problems, disturbances of motivation and social withdrawal [2–4]. Not all these deficits are obvious in common interactions, or in usual examinations. Most commonly, dysfunction is found in the patient's social interactions, particularly in relation to recreation, work, school, and home [5–7]. Adapted neuropsychological examinations are necessary in order to discover them. Commonly, the patients complain of tiredness or reduction of their efficiency. Generally, these symptoms do not persist for a long period. They are only present for several weeks or months post injury and disappear progressively after 6 to 12 months. Usually, individuals with minor cognitive dysfunction can easily reintegrate their social and

professional former condition. Nevertheless, sometimes emotional and behavioural problems may appear. There are some risk factors such as stress, fatigue, anxiety, or alcohol abuse [1,8]. Persisting problems following MHI are more common in those with previous head injury, pre-existing learning difficulties, or neurological, psychiatric, or family problems.

MHI continues to be a controversial matter regarding neurologic sequelae [9–11] or psychological sequelae [12] after minor trauma. The existent data shows patients with more severe traumas express less emotional symptoms than patients with MHI; the hypothesis is that more severe traumas disturb the ability of processing the self-consciousness. Memory deficits together with poor self-consciousness lead to easy forgetfulness of any stress agent. On the other hand, patients with MHI can have an increased self-consciousness of their own differences between how they were before and the way they are after the trauma (e.g. decreased cognitive abilities or low speed in information's processing), and increased difficulties in emotional control [13].

The clinical picture is dominated by attention and memory deficits, disfunctioning praxis, perceptual-motor abilities (especially processing speed) and changes in patient's personality and temperament that induce adaptation dificulties to daily chorus (social-educational-profesional) and lower the quality of life through the disagreeable emotional and affective feelings. Certain persons can perceive changes as repeated and unexpected failures; they will blame themselves and will probably develop a tendency to depression and anxiety. Their reduced capacity of problems solving makes them impulsive and emotionally unstable [14–16]. The increase of anxiety conducts to decrease of cognitive performances by augmentation of disabilities. The antero-retrograde amnesia and the synergetic interaction between cognitive deficits and anxiety that is installed afterwards are distinguishing MHI syndrome from the traditional posttraumatic stress syndrome. Panic is the symptom that can mediate and increase the cognitive deficits; on the other hand, it is known that patients with recurrent depression, without suffering MHI, experience deficits in cognitive processes [17].

The repeated failures, the behavioural changes keep them from readapting to their social and familial environment [7]. However, we should say that familial support and cooperation with medical personnel would facilitate the patient's reinsertion.

Irritability is a major cause for deficits in social and proffesional reintegration and in daily routine in patients with MHI. This irritability is associated with cortical lesions, but no lateralization or localization [18]. In our study, these cortical lesions are identifyed in children through psychological tests (WISC subtest "image completion" and "object assembling") but, in adults, the hipothesis isn't sustained because the abilities' deficits are generated by depression.

In children, because of the global functioning of the brain, psychical functions and processes are altered by the trauma even through microscopical lesions, but in adults, where the brain functions at a specialized level, losses aren't justified by the cerebral destructions. If neuropsychological assesments note residual deficits they express the senzitivity of the testing techniques in detecting neurobehavioural consequences of MHI even if there aren't detected neuroimagistic abnormalities. The absence of abnormalities' images is not equivalent with the absence of abnormality because microstructures can suport the damages reflected as diaskisis's effects and expressed in any kind of behaviour deficits.

Psychotherapeutical intervention is both recommended for adults and children (there are indicated strategies of family systems therapy) [19,20]. Reintegration difficulties met by the patient, child or adult, after MHI are generated by fear, affective lability, low stress tolerance and increased anxiety. These are the factors that predispose to temperamental and behavioural changes, which will gradually decrease the subject's quality of life and will have repercussions on their families. Psychotherapy is an effective intervention starting with the patient's hospitalisation.

This intervention may be included in the neurosurgeon's protocol as a unique counselling in order to inform the patient and his family regarding his evolution or as a psychotherapy program adapted to each patient, based on some individual investigations

In our study, the patients benefited of these services as a free offer, based on known post MHI evolution information and they registered in "the psychotherapy's known law of 33%": 33% refused the psychotherapy service, 33% had abandoned after few meeting and 33% took the recovery program to an end. 74% of good results were obtained in children with falls and 78% in adults with traffic accidents.

4 Conclusions

The neurosurgeon should be aware of the possibility for neuropsychological deficits after mild head injury and he should refer appropriate patients to a neurologist or psychiatrist for further evaluation and/or therapy. It is necessary to indicate a good direction for future in a simple counselling or psychotherapy program for training in stress control; this is important because MHI is considered a stressed experience and it may develops, if this is ignored, severe consequences for the patients. Of course, the severity is in terms of human efficacy and high qualitative life for him and the others in his environment.

References

1. Ettilin TM, KU, Reichmann S, et al (1992) Cerebral symptoms after whiplash injury of the neck; A prospective clinical and neuropsychological study of whiplash injury. J Neurol Neurosurg Psychiat 55:943–948
2. Goldstein N (1990) Traumatic brain injury. Neurology 27:327–328
3. Hall S, BR (1991) The relationship between intelligence and memory following minor or mild closed head injury: Greater impairement in memory than intelligence. J Neurosurg 75:378–381
4. Mittenberg W, DD, Perrin S, et al (1992) Symptoms following mild head injury: Expectation as aetiology. J Neurol Neurosurg Psychiatry 55:200–204
5. Bamrah JS, JJ (1991) Bipolar affective disorder following head injury. Br J Psychiatry 158:117–119
6. Barth J, MS, Giordani B, et al (1983) Neuorpsychological sequelae of minor head injury. Neurosurgery 13:529–533
7. Chadwick O, RM BG, et al (1981) A prospective study of children with head injury, II; cognitive sequelae. Psychol Med 11:49–61
8. Alves WM, MS, Barth JT (1993) Postconcussive symptoms after uncomplicated mild head injury. J Head Trauma Rehab 8:48–59
9. Berry H (2000) Chronic whiplash syndrome as a functional disorder. Arch Neurol 57:592–594

10. Bogduk N, TR (2000) Whiplash. The evidence for an organic aetiology. Arch Neurol 57:590–591
11. Hachinski V (2000) Whiplash. Archives of Neurology 57:594
12. Mittenberg W, SS (2000) Diagnosis of mild head injury and the postconcussion syndrome. J Head Trauma Rehabil 15:783–791
13. Fann JR, KW, Uomoto JM, et al (1995) Psychiatric disorders and functional disability in outpatients with traumatic brain injuries. Am J Psychiatry 152:1493–1499
14. Alexander MP (1992) Neuropsychiatric correlates of persistent postconcussive syndrome. J Head Trauma Rehab 7:60–69
15. Jenike MA, BA (1988) Obsessive—compulsive disorder and head trauma: A rare association. J Anxiety Disord 2:353–359
16. Jorge RE, RR, Starkstein SE, et al (1993) Depression and anxiety following traumatic brain injury. J Neuropsychiatry Clin Neurosci 5:369–374
17. Basso MR, BR (1999) Relative memory deficits in recurrent versus first episode major depression on a word-list learning task. Neuropsychological 13:557–563
18. Kim SH, MF, Kosier T, et al (1999) Irritability following traumatic brain injury. J Nerv Ment Dis 187:327–335
19. Ponsford J, WC, Rothwell A, et al (2002) Impact of early intervention on outcome following mild head injury in adults. J Neurol Neurosurg Psychiatry 55:330–332
20. Rimel RW, GB, Barth JT, et al (1981) Disability caused by minor head injury. Neurosurgery 9:221–228

Simple and Effective Assessment of Posttraumatic Higher Brain Function Disorders with Special Reference to the Prefrontal Area*

KENICHI UEMURA

Summary. Patients with prefrontal lesions present characteristic behavioral and personality disorders, but have not so far been well assessed quantitatively. We developed Hamamatsu Higher Brain Frunction Scale (HHBFS) with 9 subtests (orientation, immediate recall of 5 words, 5-minute delayed recall of 5 words, animal name listing, serial sevens, similarities, digit span, digit learning, and kana-pick-out test) as a simple and effective test battery to localize lesions within the prefrontal area Since most traumatic lesions involve wide and multiple cortical areas, we tested the validity of HHBFS using cases of a small brain tumor or infarct well localized in various parts of the prefrontal area, using magnetic resonance (MR) imageing and functional MR imaging.

Animal name listing is related to the most anterior part of the prefrontal area, kana-pick-out test and serial sevens are to the dorsolateral part corresponding to Brodmann's area 46 for working memory, digit learning with perseveration to the medial (cingulate and superiorly adjacent) area, 5-minute delayed recall to the basal prefrontal and also to the lateral temporal area. Digit learning without perseveration to the mesial tempotal area. Digit span is related to the parietal association area. HHBFS is also quite sensitive in detecting temporary minor mental disorders following stereotactic pallidotomy or thalamotomy.

Key words. Prefrontal area, Kana pick-out test, Prefrontal disorder, Predementia

Cortical localization of higher brain functions have been well studied and documented for the motor and sensory cortices and their respective associative areas covering the parietal, temporal, and occipital lobes and the posterior part of the frontal lobe. However, detailed functional localization of the prefrontal area has not yet been well documented. Here the author summarizes our clinical study of patients with localized lesions within the prefrontal area and propose our functional localization

Hamamatsu University School of Medicine, Hamamatsu, and Kato Hospital, Miyako, Iwate, Japan

* This paper was presented at the 3rd World Congress of the Academy for Multidisciplinary Neurotraumatology, held at Nagoya Marriott Asocia Hotel on March 10, 2005.

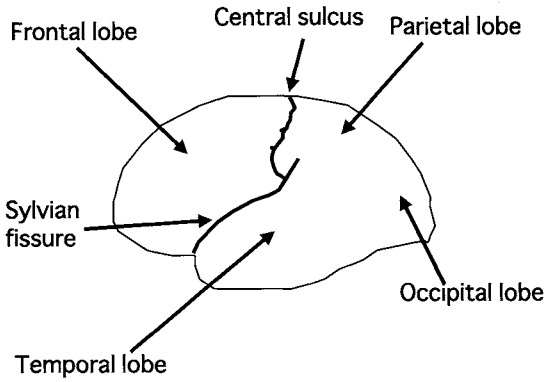


FIG. 1. A schematic drawing of the lateral aspect of the left cerebral hemisphere, indicating that there is no clear boundaries between the parietal, temporal and occipital lobes

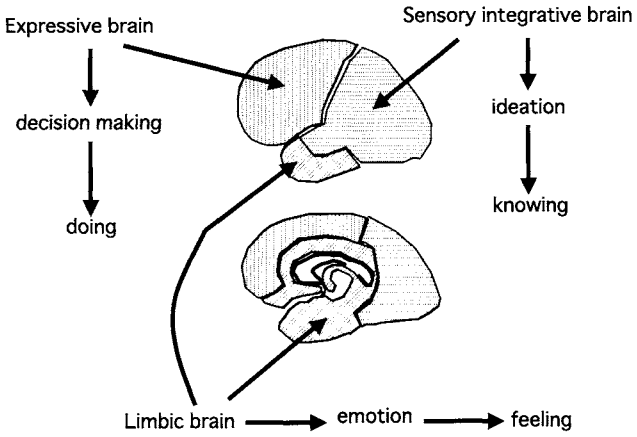


FIG. 2. Schematic illustration of the lateral aspect of the left cerebral hemisphere (above), and the medical aspect of the right cerebral hemisphere, indicating that the cerebral hemisphere can be functionallty divided into three parts: the sensory integrative brain, the limbic brain and the expressive brain

of this particular area based on our new test battery of Hamamatsu Higher Brain Function Scale.

1 Three Divisions of the Cerebral Hemisphere

The cerebral hemisphere has anatomically been divided into the frontal, temporal, parietal, occipital and limbic lobes. As shown in Fig. 1, the central sulcus divides the frontal from the parietal lobe, and the Sylvian fissure divides the frontal from the temporal lobe. However, there is no clear division between the parietal, temporal and occipital lobes, indicating that they function as a whole. In fact, the temporal lobe is not existent in lower animals, being present only in primates.

From the standpoint of functional localization, the human cerebral hemisphere can well be divided into three parts, the posterior "sensory integrative brain", the medial "limbic brain", and the frontal "expressive brain", as shown in Fig. 2. The sensory inte-

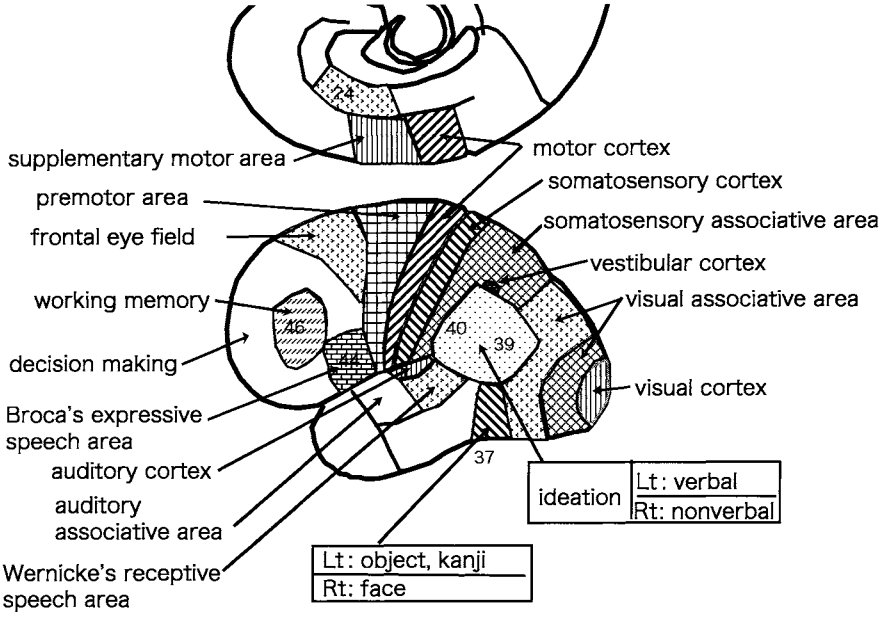


FIG. 3. The lateral aspect of the left cerebral hemisphere indicating known cerebral functional localization. The upper figure shows the upper part of the medical aspect of the left cerebral hemisphere shown upside down to show the supplementary motor area. The numbers represent Brodmann's areas

grative brain integrates our perceptions through various sensory systems, including auditory sensations perceived in the temporal lobe, somatosensory sensations perceived in the parietal lobe and visual sensations perceived in the occipital lobe, for ideation and knowing. The limbic brain is related to our emotion and feeling. The expressive brain is related to our decision making and behavior, and our doing. Now you are reading this paper. If you feel interested in it, you decide to read it till the end. However, if you do not feel interested, you decide to stop reading right now.

2 Summary of Known Cortical Localization

As shown in Fig. 3, cortical localization of higher brain function has been well documented for the sensory integrative brain and for the posterior part of the frontal lobe related to motor and speech functions, but not for the prefrontal area.

Somatosensory sensations are perceived at the somatosensory cortex (postcentral gyrus, Brodmann's areas 3, 1, and 2) whose dysfunction can best be detected by two-point discrimination, and the perceived information is further processed in the adjacent somatosensory associative area (Brodmann's areas 5 and 7), whose dysfunction results in astereognosis. Visual sensations are perceived at the visual cortex (Brodmann's area 17) whose dysfunction results in homonymous visual field defects. The

perceived visual information is further processed in the adjacent visual associative area (Brodmann's area 18 and 19). Its dorsal part is responsible for cognition of visuospatial orientation, while its temporal part, particularly at Brodmann's area 37, is responsible for cognition and identification of objects on the dominant hemisphere and that of face on the nondominant hemisphere. Auditory sensations are perceived at the auditory cortex (Brodmann's area 41) where tunes are perceived, and the information is processed in the adjacent auditory associative area (Brodmann's area 42), where the anterior part is related to cognition of tone color and voice, and the posterior part is responsible for conginition of the meaning on the dominant hemisphere as will be described in more detail below.

The major parietal associative area (Brodmann's areas 39 and 40) integrates all the sensory information for verbal ideation on the dominant hemisphere and for visuospatial ideation on the nondominant hemisphere.

As for the posterior portion of the frontal lobe, the motor cortex (Brodmann's area 4) is responsible for volitional contraction of topographically specific muscles. The premotor area (Brodmann's area 6) just anterior to the motor cortex on the lateral surface of the hemisphere is responsible for visually or externally guided movements. The supplementary motor area (Brodmann's area 6) just anterior to the motor cortex on the medial surface of the hemisphere is responsible for memory-guided automatic movements, where complex trained motor patterns are stored. The frontal eye field (Brodmann's area 8) just anterior to the premotor area is responsible for volitional eye movements.

Many psychological tests for intelligence, aphasia, agnosia and apraxia are good only for the sensory integrative brain and the posterior frontal area.

3 Cortical Localization for Language Function

As shown in Fig. 4, the posterior portion of the auditory associative area on the dominant hemisphere is the Wernick's receptive speech area where the meaning of the heard words are understood. Brodmann's area 44 is Broca's expressive speech area responsible for speaking. Letters perceived in the visual cortex are sent to other higher centers for interpretation. Phonetic letters such as alphabets, kanas, and Hungle letters (Korean kanas) are interpreted at Brodmann's area 39, while ideographic letters like kanjis are interpreted at Brodmann's area 37.

Ojeman stimulated Wernicke's speech area of about 14 bilingual patients and found that bilinguals have two separate areas for two different languages without exception. Figures 5 and 6 show the results of our study of one nonbilingual and one bilingual persons who listened to English and Japanese news during functional magnetic resonance imaging. As shown in Fig. 5, in the nonbilingual, one and the same area was activated while listening to the two languages. However, as shown in Fig. 6, in the bilingual, the posterior part of Wernicke's receptive speech area was activated while listening to Japanese while the anterior part was activated while listening to English. Figure 7 shows the lateral aspect of the left hemisphere in the bilingual, showing two areas for respective two languages.

Table 1 shows the degree of lateralization of speech function tested in 32 volunteers by electroencephalographic topography [1].

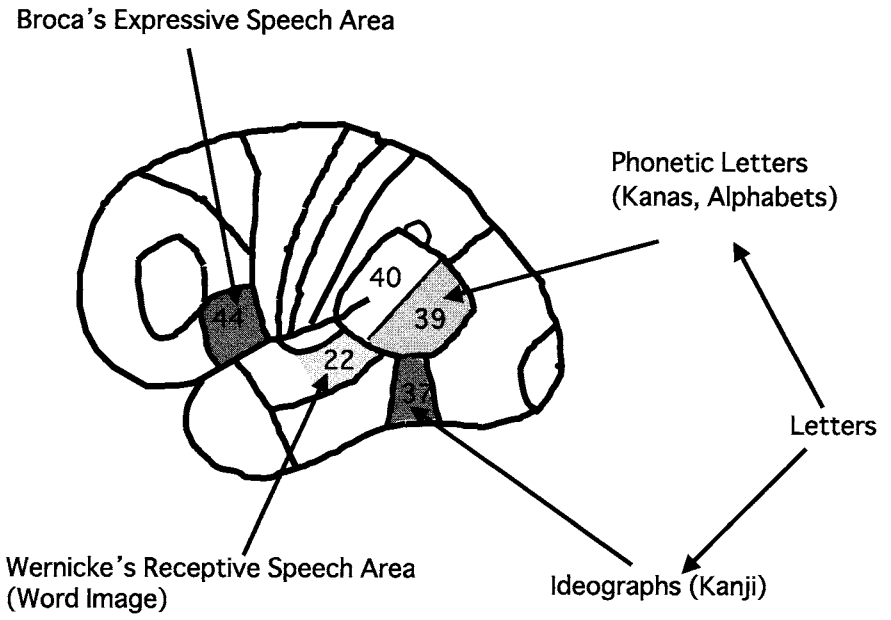


FIG. 4. The lateral aspect of the left cerebral hemisphere showing language-related areas

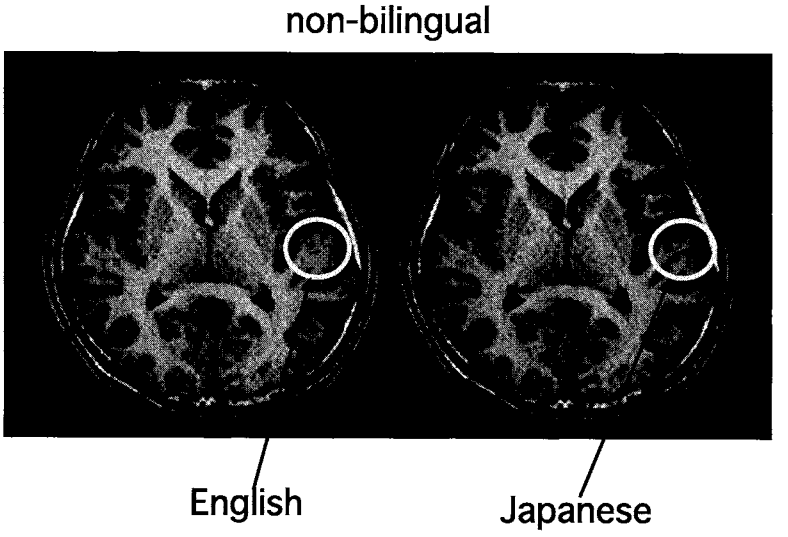


FIG. 5. Functional magnetic resonance (fMR) images of a non-bilingual, while listening to English news on the left, and while listening to Japanese news on the right. The same area was activated, and the subject did not understand the English news at all

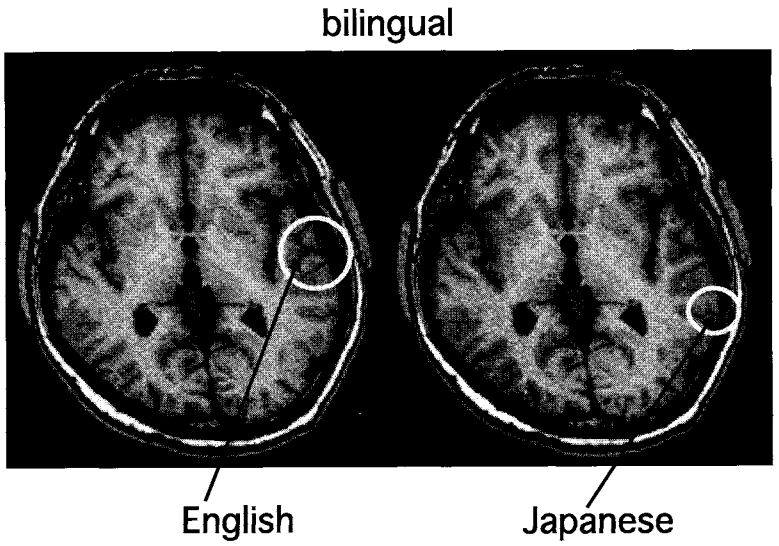


FIG. 6. fMR images of a bilingual, while listening to English news on the left, and while listening to Japanese news on the right. Note that the area activated by English is located anterior to that activated by Japanese, indicating that the bilingual has separate areas for respective languages

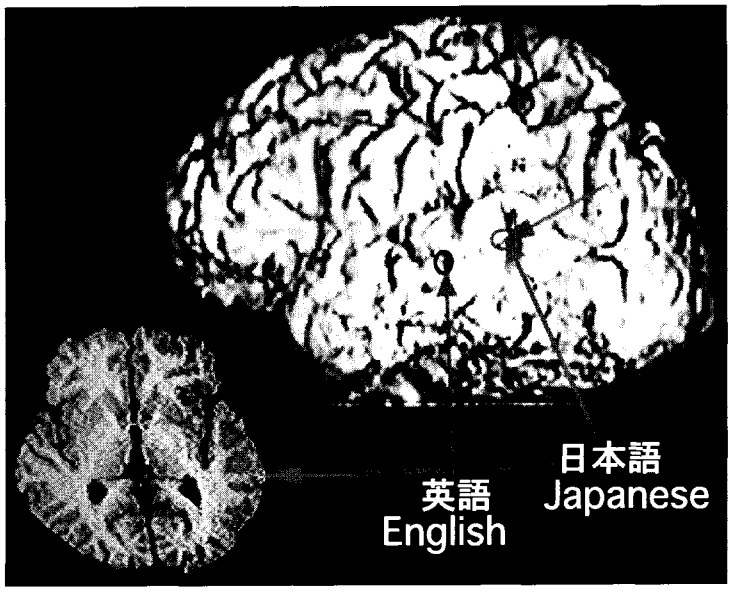


FIG. 7. The lateral aspect of the left cerebral hemisphere of the bilingual shown in Fig 6, indicating the area for English is anterior to that for Japanese

handed	dominant hemisphere			total
	right	left	bilateral	
right	2 (8.7%)	12 (52.2%)	9 (39.1%)	23
left	1 (11.7%)	3 (33.3%)	5 (55.6%)	9
total	3 (9.4%)	15 (46.9%)	14 (43.8%)	32

TABLE 1. Lateralization of speech function

4 Early Detection of Mild Prefrontal Dysfunction

Patients with prefrontal lesions present characteristic behavioral and personality disorders, but their cognitive dysfunctions have not so far been well assessed quantitatively.

More than 20 years ago we became interested in developing a test battery useful for "early detection of mild prefrontal dysfunction". A mild prefrontal dysfunction is characterized by inability of simultaneous conduction of multiple tasks. So Dr. Mitsuo Kaneko, one of our colleagues, developed a "kana pick-out test" to detect this inability.

As shown in Fig. 8, Japanese letters consist of kana and kanji. The kanji consists of thousands of ideographic letters, while the kana consists of 46 phonetic letters, among which 5 represent vowels, 40 represent consonants and vowels, and 1 represents a consonant.

Japanese sentences are usually written with kana and kanji, but can be written with kana alone. In the kana pick-out test, we ask the patient to read a story written only with kana, to circle all the vowel kana: a, i, u, e, o, to remember the story to report later, and to complete the task within one minute (Fig. 9).

As shown in Fig. 10,「むかし」(mu-ka-shi) "at one time",「あるところに」(a-ru-to-ko-ro-ni)"at a certain place", now here you must circle「あ」(a),「ひとりぐらしの」(hi-to-ri-gu-ra-shi-no)"a solely living",「おばあさんが」(o-ba-a-sa-n-ga)"old woman was", now here you must circle「お」(o) and「あ」(a). The correct response is shown in Fig. 11.

We conducted this test to 352 normal volunteers with different ages and obtained the age-related score distribution as shown in Fig. 12. The average score decreases with aging, but with fairly constant standard deviations.

We conducted this test and the minimental status examination to 70 elderly volunteers, and found that the kana pick-out test is very sensitive to detect predementia

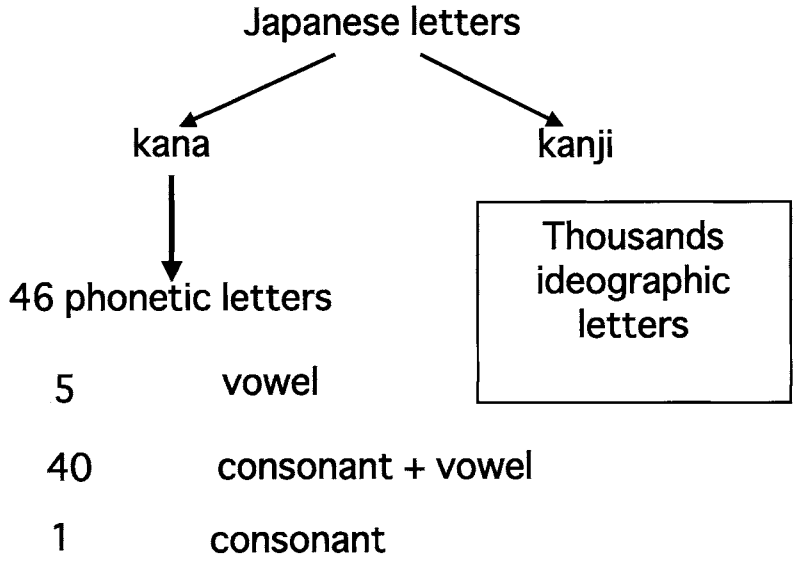


FIG. 8. To be changed to Table 1: Degrees of lateralization of speech in 32 volunteers tested by electroencephalographic topography. Amplification of beta waves rather than suppression of alpha waves was used to detect the areas activated by verbal or non-verbal tasks. See reference 1

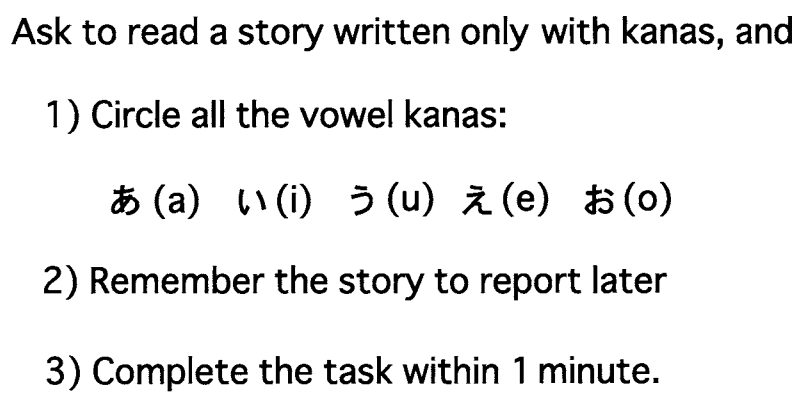


FIG. 9. Kana pick-out test

with normal MMS scores (24 or above) but with poor kana pick-out scores (10 or below), as shown in Fig. 13.

Finally we developed Hamamatsu Higher Brain Frunction Scale (HHBFS) with 9 subtests as a simple and effective test battery to localize lesions within the prefrontal area. As shown in Tables 2–4, the substests consist of (1) orientation, (2) immediate recall of 5 words of toothbrush, coin, knife, fan and fork, (3) 5-min delayed recall of the 5 words, (4) animal name listing, requesting listing up more than 10 animal names

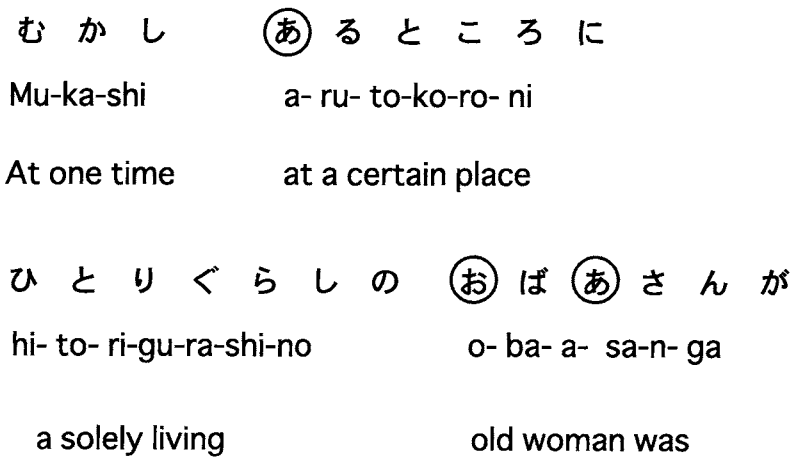


FIG. 10. Kana pick-out test

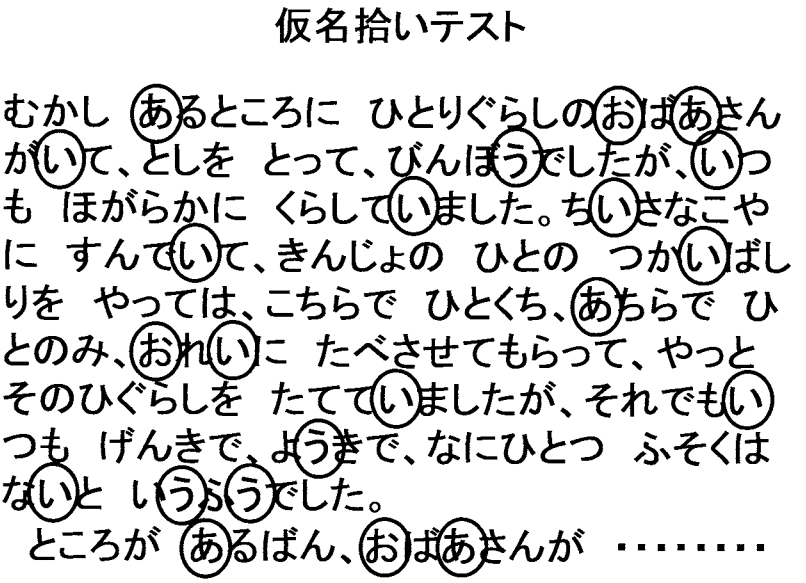


FIG. 11. Kana pick-out test

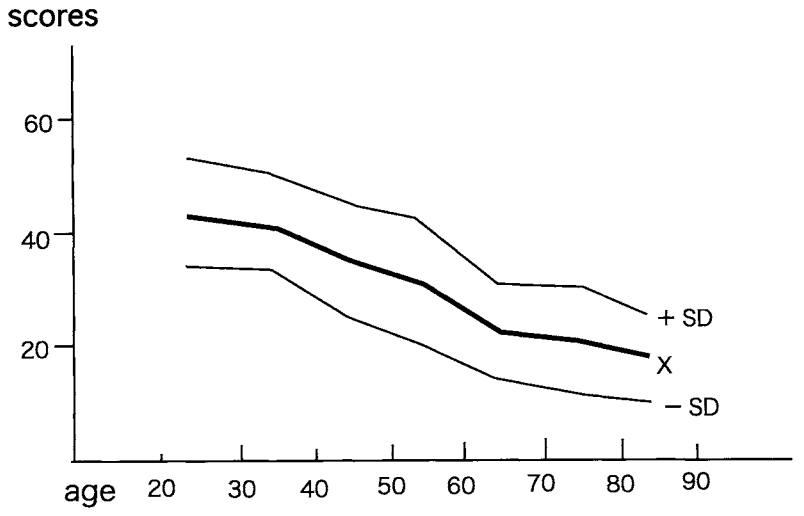


FIG. 12. Kana pick-out test. 352 normal age-related score distribution

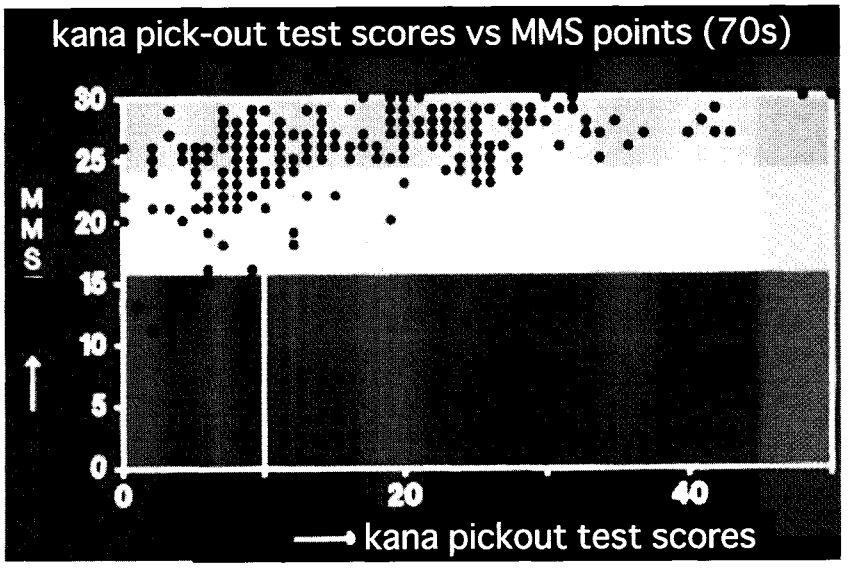


FIG. 13. Kana pick-out-test scores *vs* MMS points (70 s)

1) Orientation

2) Immediate recall of 5 words
toothbrush, coin, knife, fan, fork

3) 5-minute delayed recall of the 5 words

4) Animal name listing (≧10/minute)

5) Serial sevens (serial substraction of 7 from 100)

TABLE 2. Hamamatsu Higher Brain Function Scale

6) Similarities
(1) dog & lion
(2) ax & saw
(3) orange & banana
(4) north & west
(5) poem & statue
(6) house & ship
(7) goldfish & pine

7) Digit span

8) Digit learning

TABLE 3. Hamamatsu Higher Brain Function Scale

within one minute, (5) serial sevens (serial subtraction of 7 from 100), (6) similarities between dog and lion, ax and saw, orange and banana, north and west, poem and statue, house and ship, and goldfish and pine, (7) digit span, (8) digit learning and (9) kana-pick-out test for nonsense phrases and for a story. When experienced, one can conduct HHBFS in 15 min.

We obtained averages and standard deviations of this test from 40 normal volunteers with different ages from 10 to 79, as shown in Fig. 14. Since most traumatic lesions involve wide and multiple cortical areas, we tested the validity of HHBFS using

9) kana pick-out test → (1) nonsense phrases
(2) a story

15 minutes

Useful for quick postoperative assessment

TABLE 4. Hamamatsu Higher Brain Function Scale

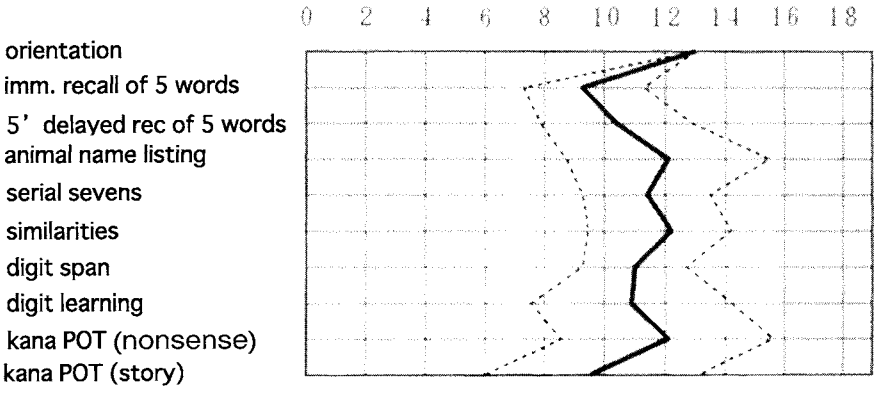


FIG. 14. HHBFS for 40 normals, age 10–79 (44.9 ± 19.2)

cases of a small brain tumor or infarct well localized in various parts of the prefrontal area, using magnetic resonance (MR) imaging and functional MR imaging.

For a lesion well localized in the dorsolateral prefrontal area (Fig. 15), the score was very low for animal name listing, and slightly low for serial sevens and similarities (Fig. 16). For a lesion well localized in the medial prefrontal area (Fig. 17), the score was zero for digit learning because of perseveration, but not because of memory disturbance, and slightly low for serial sevens (Fig. 18). For a lesion well localized in the orbital prefrontal area (Fig. 19), the score was quite low for kana pick-out test and slightly low for animal name listing (Fig. 20).

A functional MR imaging (Fig. 21) showed that the auditory kana pick-out test is related to Brodmann's area 46 for working memory in the dorsolateral prefrontal area The animal name listing was also localized to the same area, as shown in Fig. 22.

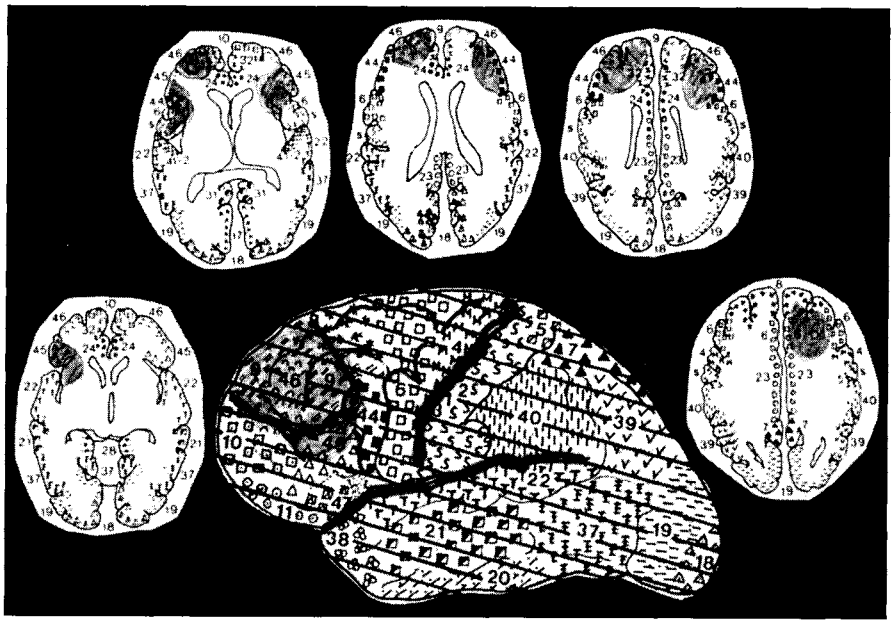


FIG. 15.

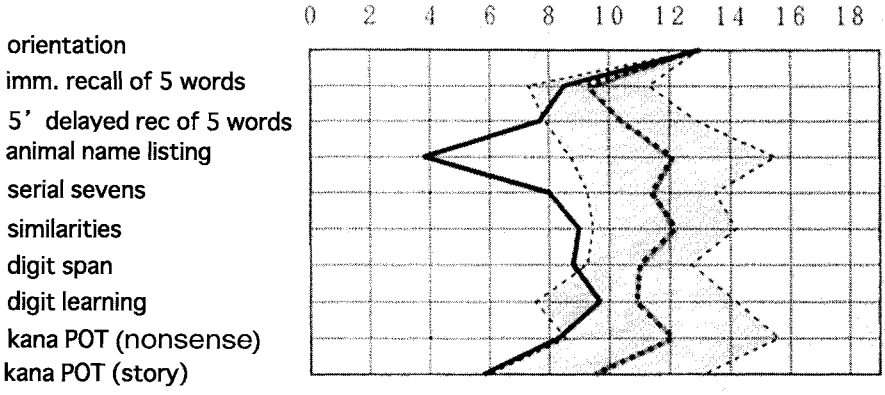


FIG. 16. Hamamatsu Higher Brain Function Scale (HHBFS), dorsolateral prefrontal lesions, right 3, left 3

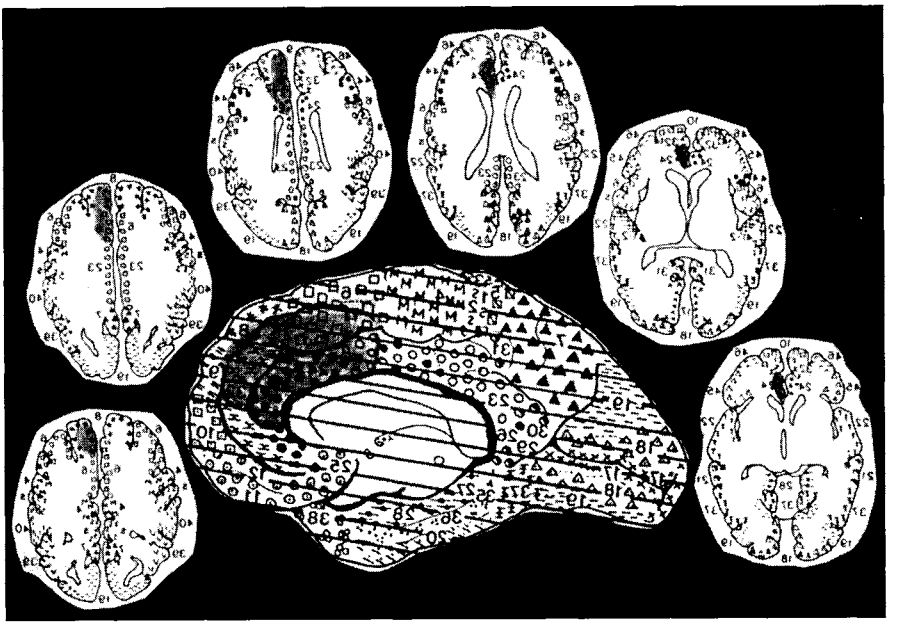


FIG. 17.

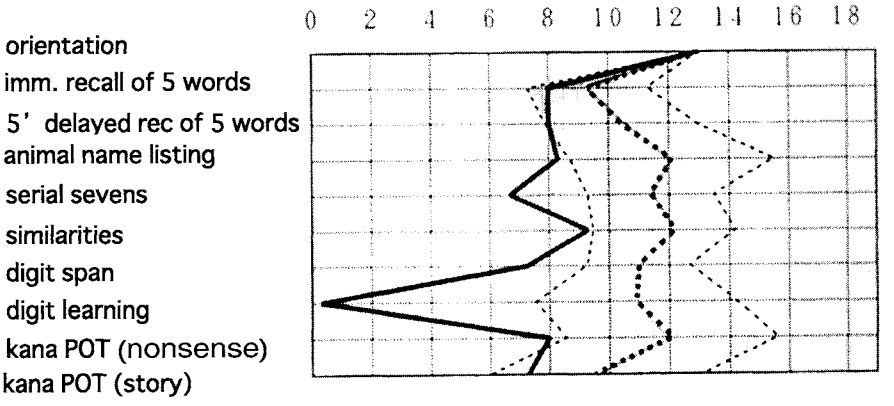


FIG. 18. Hamamatsu Higher Brain Function Scale (HHBFS), medial prefrontal lesions, left 3

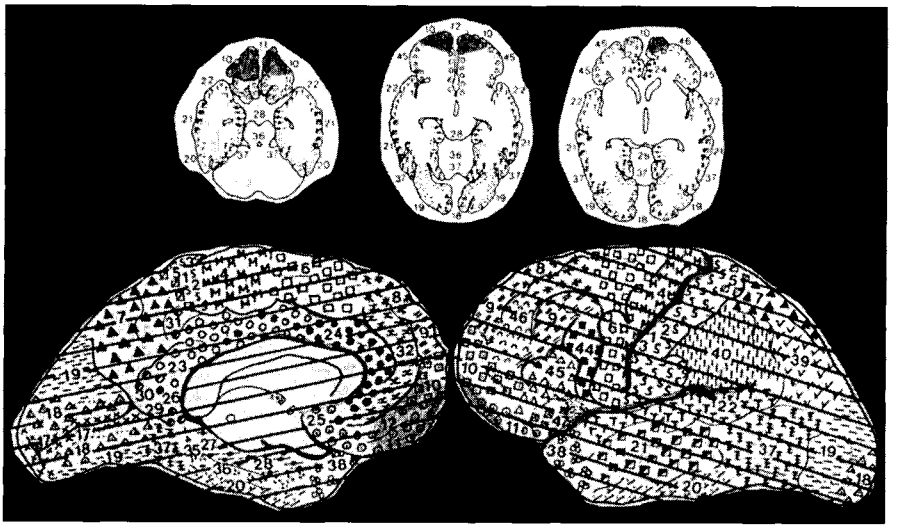


FIG. 19.

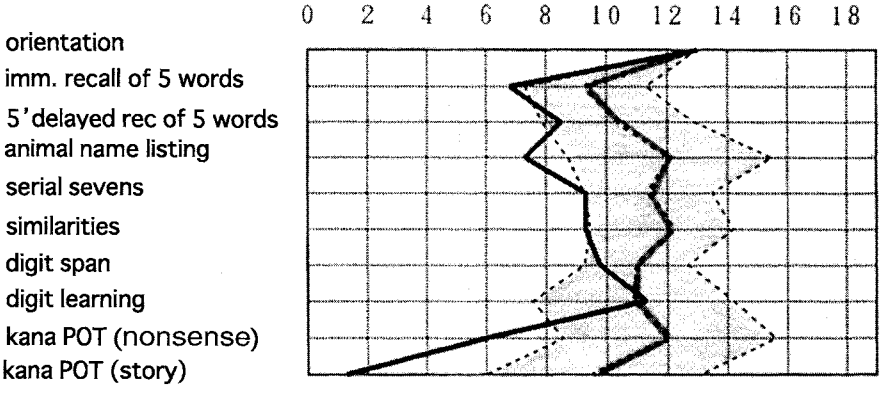


FIG. 20. Hamamatsu Higher Brain Function Scale (HHBFS), orbital prefrontal lesions, right 3, left 1

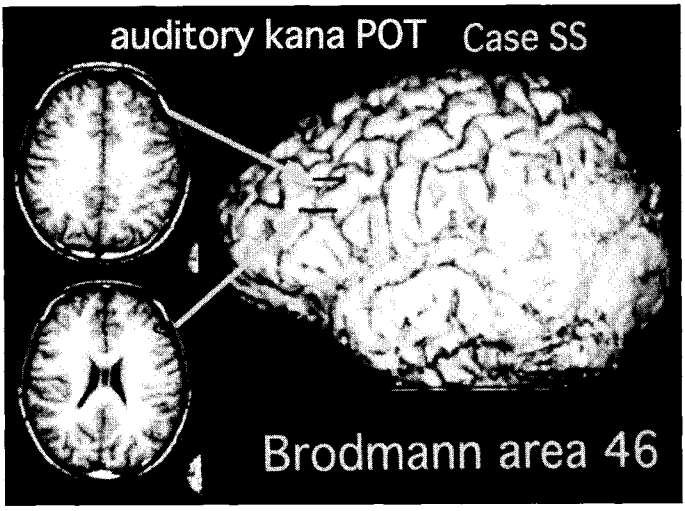

auditory kana POT Case SS
Brodmann area 46

FIG. 21.

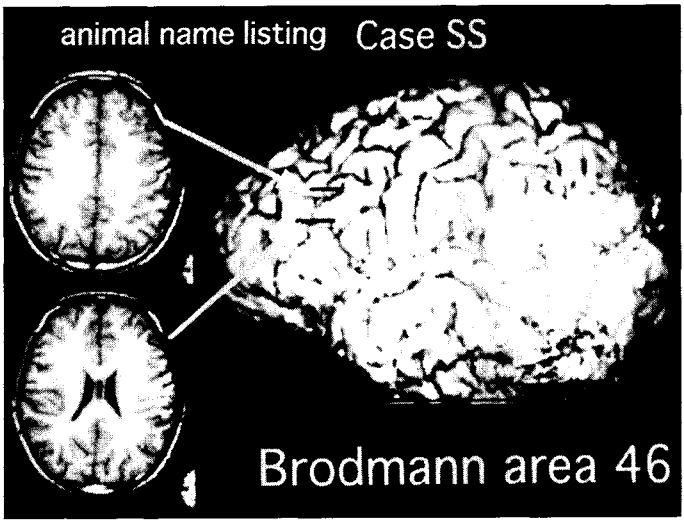

animal name listing Case SS
Brodmann area 46

FIG. 22.

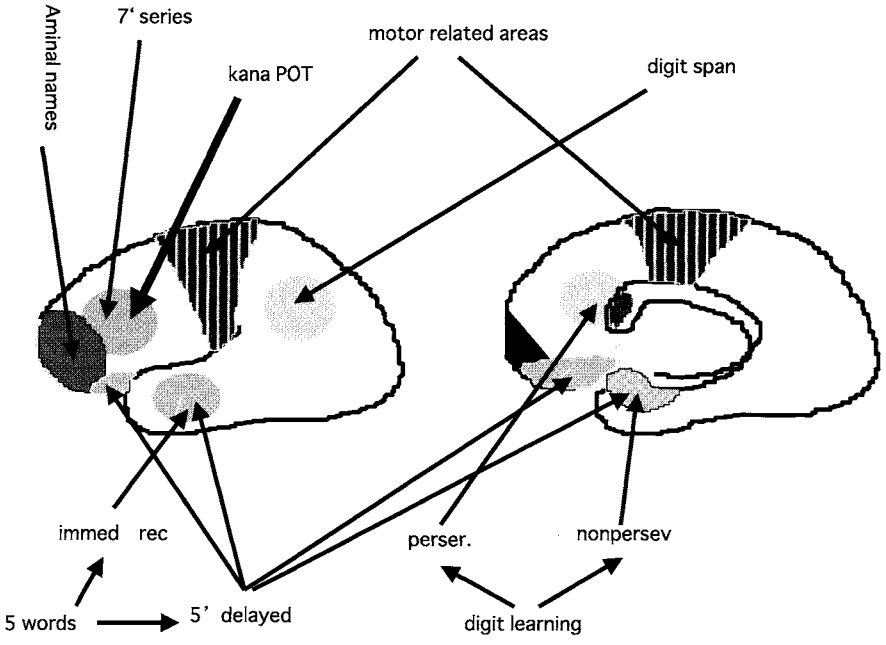


FIG. 23.

5 Proposed Functional Localization of the Prefrontal Area

Figure 23 shows the summary. Motor-related areas are in the motor cortex, the premotor area, and the supplementary motor area. Digit span is related to the parietal associative area. Digit learning with perseveration is related to the cingulated area, while digit learning without perseveration is related to the medial temporal area. As for recalling 5 words, the immediate recall is related to the lateral temporal area, while 5-min delayed recall is related to the lateral temporal, the basal frontal and the medial temporal areas. Animal name listing is related to the anterolateral frontal area Serial sevens is related to the dorsolateral area, and kana pick-out test is also related to the dorsolateral area.

Reference

1. Uemura K, Imamura Y, Kaneko M (1996) Clinical neuropsychology for memory and intelligence. Jpn J Neuropsychol 12:11–29

Neurobehavioral Sequelae in Neurotraumatology

ANNE-LISE CHRISTENSEN

Summary. The neurosurgical treatment in neurotraumatology has progressed dramatically in later time; neurosurgeons have developed still more efficient treatment procedures, resulting in survival of even severely injured patients.

However, in their late recovery many of these patients are described as experiencing severe social difficulties. They loose their social status, many get divorced or the families get into trouble. Stereotypes like social disadvantage, personality changes, and irreparable cognitive deficits have prevailed in the literature as characteristic, unavoidable neurobehavioral sequelae. Rehabilitation efforts have most often been considered expensive and ineffective.

More lately, progress in neuroscience has given evidence of as well brain plasticity as brain repair, findings supportive of the possibilities of functional improvement. Moreover insight in neural network theories underlying brain function has lead to the understanding that treatment/reeducation in order to become effective has to be planned individually.

In the paper, I shall advocate for the importance of a close collaboration in the multidisciplinary team during the recovery progress, where the advancements in neuroscience are integrated and where neuropsychological insight is made use of in the understanding of the individual patients' functioning and behavioral reaction patterns. It is only through a comprehensive treatment, where medical, physical and neuropsychological factors are incorporated that the optimal goal—a constructive, fulfilling life after brain injury—can be achieved.

Key words. behavioral sequelae, brain plasticity, individuality, neuropsychological rehabilitation

Center for Rehabilitation of Brain Injury, University of Copenhagen, Njalsgade 88, 2300 Copenhagen K, Denmark

1 The Present Concept of Neurobehavioral Disability

The literature dealing with the immediate and long term cognitive and behavioral consequences after brain injury is extensive. Books and articles from the 1970s and 80s [1–4], are repeatedly quoted and new research performed with updated methods. In the introduction to several of these publications it is stated that the awareness of numerous and varied neurobehavioral sequelae is increasing, and that they exert the largest influence on the injured individual's functioning and ability to reintegrate into community: the term "neurobehavioral disability" has grown in use to denote this, often permanent, complex, subtle, yet pervasive constellation of cognitive—behavior changes. The elements the term comprises are: executive dysfunction, deficits of attention, diminished insight, poor social judgment, labile mood, problems of impulse control, as well as a range of personality changes which, when combined with specific cognitive problems and pre-morbid personality characteristics, lead to a serious social handicap, undermining the person's capacity for independent social behavior.

Wood [4] makes an attempt to categorize the disabilities and presents three categories that he finds "reasonably good operational distinctions for examination"; the three are: (1) disorders of drive, arousal, and motivation, (2) diminished inhibitory or regulatory control and (3) altered personality. He concludes that the categories are not mutually exclusive and usually combine in ways that undermine a person's capacity to interact reliably with the social environment.

In a description given by Lezak [3] the term "personality change" is more elaborated. Inclusion of social perceptiveness with egocentricity and lack of empathy, social sensitivity and self-reflective skill is proposed; added to the list are impairments in control, insight and self-regulation; specific emotional changes such as apathy and irritability; and an impaired capacity to profit from previous experience. Lezak also provides a definition of the term "altered personality": "Although vague, it indicates a change from some assumed pre-morbid condition, without pointing to the nature of the change itself." For her, the notion of personality change includes all the cognitive and behavioral changes already described plus changes in emotional expression, cognitive interpretation, and behavioral disposition.

1.1 The Cerebral Basis of the Neurobehavioral Disabilities

The agreement that the frontal structures and their complex connections with a range of cortical and sub cortical centers are important for the higher cortical functions, for control and planning go far back [5]. Also the fronto-temporal structures have been shown to be influential.

A case story that has gained long lasting interest and has been described in several books and papers is the case of Phineas Gage, who suffered a bilateral lesion of the ventromedial prefrontal cortex, when an iron bar penetrated his brain [6]. As the description goes, the man did not lose his intellect, but "he was no longer Gage".

1.2 Characteristics of Patients Showing Neurobehavioral Disabilities

In the description of these patients it is characteristic that they have usually spent only brief periods in neuro-rehabilitation units. Their problems emerge later in recov-

ery, having a serious impact on social recovery, measured in terms of the individual resuming work, maintaining his/ her role in the family and relating to others in appropriate and meaningful ways.

2 Considerations about the Concept "Neurobehavioral Disabilities"

Reviewing the research about the consequences of brain injury it is evident that the outcome of severe injury to the central nervous system is so far from any optimism, that it seems reasonable to ask the questions: (1) Is it realistic that there is no or only very little hope for treatment and recovery from brain damage and (2) How do the latest neuroscientific research findings about neuroplasticity and brain repair match this pessimistic concept. (3) Has the existing concept obtained a status which reins undisputed and is it so that specific prejudices prevent physicians and scientists from exploring new directions in therapy or considering alternative views about how the brain works? A possibility could also be lack of communication between scientists and practitioners—lack of multidisciplinary collaboration

3 An Attempt to Introduce A Change of Concept

According to the neurologist Kurt Goldstein, who worked with brain injured soldiers during World War I [7] it is in principle faulty to try to make a distinction between so-called organic and functional diseases, as far as symptoms and therapy are concerned. In both conditions, one is dealing with abnormal functioning of the same psychophysical apparatus and with the attempt of the organism to come to terms with that. The concern should be a description of the symptoms and an interpretation of the behavioral changes, particularly in respect to the patient's personality.

3.1 Goldstein's Description of the Symptoms of Brain Damage

According to Goldstein, change of personality is only one factor in the complex effect of various factors: (1) Inborn patterns of behavior in special fields—such as motor and sensory patterns, (2) Expressions of the so-called catastrophic conditions and (3) expressions of protective mechanisms.

Personality shows itself in behavior, it is the mode of behavior of a person in terms of its particular capacities, behavior is always an entity and concerns the whole personality, and it can only in an abstractive way be separated into parts—bodily processes, conscious phenomena, states of feelings, attitudes and so on.

All phenomena of behavior become understandable only if it assumed that the behavior of the "Organism" is determined by one trend: the trend to actualize itself, its nature and its capacities. In a situation of success the behavior is ordered, in a situation of failure it is disordered or catastrophic. For the brain injured person failure means the impossibility to of self-reassurance and existence, which produces anxiety, and when self-realization is seriously in danger, catastrophe may occur together with severe anxiety—an inner state on cannot flee from—and a group of symptoms or behavior changes are developed, which makes it possible for the patient to get rid of the catastrophic condition—of the anxiety.

3.2 Reaction Patterns as Protection

It is the changes of behavior that make it possible for the patient to avoid the tasks that cannot be coped with. Examples are to withdraw from stimuli and company, to keep up orderliness in every respect to stick to arrangement that can be managed. Lack of awareness is the most effective exclusion.

Adopting Goldstein's theory creates a possibility to analyze the patient's reactions in depth, which again can provide an insight that can add to the planning of therapeutic procedures in agreement with the actual state and experiences of the patient. Explanation and feed back to the patient about the characteristic behavior reactions may help the patient to understand and thereby lead to improvement.

3.3 Evidence of Intervention

Very late outcome study after focal wartime brain wound [8] refers remarkably good results both with respect to preservation of cognitive function and social adaptation. There was little difference in self-report on rating scales between veterans after World War II and controls. Cognitive data showed striking preservation, behavioral outcome was good and there was rarely evidence of psychiatric problems.

The neuropsychologist Freda Newcombe, who performed the study, attributes the result to a number of factors: expert and systematic medical care, initiated within hours of wounding, the psycho-social context and intensive, close and long term monitoring of progress, physically, emotionally and socially. The study emphasizes and should reinforce the crucial importance of aftercare.

3.4 Influences from Neuroscience

The new trends that need to be taken into consideration are brain plasticity and brain repair [9] as well as the network theory [10] illustrating the brains functional systems and recognizing the individual variances in brain structure and networks. Also the application of advanced imaging technique has provided insight that serves rehabilitative efforts. The importance of early intervention has been shown, the importance of adapting appropriate methods at the right times, leveling training by feed back and stimulating support and offer a wide scope of therapy, where ecological and environmental factors are taken into account.

4 Rehabilitation Principles

Advanced, comprehensive rehabilitation programs came on the scene in the US and in Europe in the late 1970s and 80s. In the US the first of the so-called holistic centers were located at the New York University School of Medicine, inspired by experiences in Israel of Leonard Diller and Yehuda Ben Ishay [11]. George Prigatano has started centers in Oklahoma and Phoenix, based on ideas later published in his "Principles of Rehabilitation" [12]. In Europe the "Center for Rehabilitation of Brain Injury" (CRBI) at the department of Psychology, the University of Copenhagen became the first [13]. The shared principles of this concept mainly deal with the planning of individualized programs, based on information about current and premorbid functions—physical,

cognitive, and social—adapted in accordance with the patient's insight, undergoing dynamic changes according to the development and improvement. The phenomenological, interactive contact with the patient makes it possible to stress the hard work, regaining functional independence is, at the same time as goals and hopes for the future can be included [14]. The rehabilitative efforts contain early and active involvement, stimulation from the environment, and working together with others. An issue that has proven to be of special importance is the support, which can be gained if therapists and families believe in the potential power of training and relearning.

In this respect a thought provoking quotation from the American neurologist Shepherd Ivory Franz working with brain injured soldiers during the World War II [15] seems relevant: "Relatives who only bemoan the fate of a man in need of reeducation, who pity him and regard him as a helpless burden, place a real obstacle in way of his recovery. The family which encourages its patient-member, which makes him plans for the day, when he shall be "recovered", which regards him as a potential asst instead of a burden, and which cooperates with the instructors in charge of the patient, is a potent factor in the eventual recovery (p 44).

In [9] Donald Stein refers the quotation (p 331) supporting the attitude on the basis of his research in brain plasticity and continues the quotation: "The production of a sound, normal mental attitude in the patient must have a primary place in all reeducation work. It is an integral part of rehabilitation in all its stages. An attitude of hope and hopefulness must be created if it does not exist" (p 44).

4.1 Development of Evaluation Questionnaire: QOLIBRI

With the purpose of learning about the brain injured patient's own experiences a new questionnaire has been developed by an international group and is at present under statistical evaluation. The data of the Danish group have been convincing regarding the patients' experiences of regaining functional independence and also their feelings of satisfaction with what they express as improved general capacities. Interesting in this respect is their appreciation of the rehabilitation they have received. Statements such as "I feel that I have done great progress over the last nine years after rehabilitation" or "I am happy for my rehabilitation: they took me by the hand and helped me reach my goals".

5 Answers to the Initial Questions Regarding Life after Brain Injury

The questions regarding a domineering pessimistic attitude and possible prejudices can be answered confirmatively. The concepts of plasticity and brain repair cannot be overlooked any longer and the growing awareness of the importance of stimulation, learning and feed back provided in an interactive atmosphere must be emphasized.

Over all, at the present time it should be possible to obtain agreement, that enough evidence exits in favor of early, individualized, stimulating treatment, supported by an optimistic attitude and social acceptance.

What is lacking is maybe belief in the power of a true and open collaboration, where all the professionals who are needed in the complex process of the reeducation of the injured brain are recognized and integrated in accordance with what they each have the possibility to contribute.

References

1. Bond MR (1975) Assessment of the psychosocial outcome after severe head injury. CIBA Found Symp 34:141–157
2. Brooks N (1984) Head injury and the family. In: Brooks N (ed.) Closed head injury: Psychological, social and family consequences. Oxford University Press, Oxford
3. Lezak MD (1978) Living with the characterologically altered brain injured patient. J Clin Psychiatry 39:592–598
4. Wood RLl (2001) Understanding neurobehavioral disability. In: Wood RLl, Mc Millan TM (eds) Neurobehavioral disability and social handicap? pp 2–27
5. Luria AR (1965) Higher cortical functions in man. Basic Books, New York
6. Damasio H, Grabowski T, Frank R, Galaburda AM, Damasio AR, et al (1994) The return of phineas gage: Clues about the brain from the skull of a famous patient. Science 264:1102–1105
7. Goldstein K (1952) Effect of brain damage on the personality. Psychiatry 15:245–260
8. Newcombe F (1996) Very late outcome after focal wartime brain wounds. J Clin Exp Neuropsychol 18:1–23
9. Finger S, Stein DG (1982) Brain damage and recovery. Research and clinical application. Academic Press, New York
10. Edelmann GM, Mountcastle VB (1978) The mindful brain. Plenum Press, New York
11. Ben-Yishay Y, Ben-Nachum Z, Cohen A, et al (1978) Digest of a two-year comprehensive clinical rehabilitation research program for out-patient head injured Israeli veterans (Oct.1975 to Oct. 1977). In: Ben-Yishay Y (ed.) Working approaches to remediation of cognitive deficits in brain damaged persons, (Rehabilitation Monograph No.59). New York University Medical Center, Institute of Rehabilitation Medicine, New York
12. Prigatano GP (1999) Principles of neuropsychological rehabilitation. Oxford University Press, Oxford
13. Christensen AL, Pinner EM, Møller Pedersen P, et al (1992) Psychosocial outcome following individualized neuropsychological rehabilitation of brain damage. Acta Neurol Scand 85:32–38
14. Christensen AL (2000) Neuropsychological postacute rehabilitation. In: Christensen AL, Uzzell BP (eds) International Handbook of neuropsychological rehabilitation. Kluwer Academic/Plenum Publishers, New York
15. Franz SI (1923) Nervous and mental re-education. Macmillan, New York

Clinical Analysis of the Patients with Anterior Skull Base and Craniofacial Injury in the Acute Head Trauma

Yoji Node[1], Tomonori Tamaki[1], and Akira Teramoto[2]

Summary. During past 8 years, we have encountered 204 cases of front-facial injuries. They were divided into three groups, that is, skull base injury (SB: 69), craniofacial injury (CF: 124), and skull base and craniofacial injury (SC: 11). The cause of trauma was traffic accident in 114 cases, fall in 63, fight in 18, and others in 9. Glasgow coma scale on admission was as follows: SB 8.7, CF 12.6, SC 10.6 (mean GCS: 11.1). Surgery was performed in each group (29 SB, 59 CF, 8 SC), respectively. Prognosis (good, poor, dead) of the patients was as follows: SB (30, 15, 24), CF (106, 12, 6), SC (6, 3, 2). In the Group SB, surgery was performed on 29 cases. Of 29 cases, 11 had external decompression and/or removal of hematoma, 4 ligation of external carotid artery (ECA), 4 anterior skull base reconstruction (ASR), 1 embolization of ECA, and others. In the Group CF, open reduction and internal fixation (ORIF) was done in 58 and ASR in one. In the Group SF, ORIF was done in 3 cases, craniotomy in 3, ECA ligation in one, and ECA embolization in one. Cause of death was multiple trauma and severe meningitis.

Key words. anterior skull base injury, craniofacial injury, frontobasal fracture

1 Introduction

Anterior skull base and craniofacial injury, combined with brain injuries and dural tears, constitute a frequent pattern of injury when major anterior craniofacial trauma occurs [1–3]. During past 8 years we experienced 204 cases with anterior skull base and craniofacial injury, and analyzed their way of injury, cause of trauma, prognosis, and treatment.

Department of Neurosurgery, [1]Nippon Medical School Tama Nagayama Hospital, 1-7-1 Nagayama, Tama, Tokyo 206-8512, Japan, and [2]Nippon Medical School, Bunkyo-ku, Tokyo, Japan

TABLE 1. Cause of trauma in the patients with anterior skull base and craniofacial injuries

	SB	CF	SC	Total
Traffic accident	36	68	10	114
Fall	30	32	1	63
Fight	1	17	0	18
Others	2	7	0	9
Total	69	124	11	204

SB, anterior skull base injury; CF, craniofacial injury; SC, anterior skull base and craniofacial injury.

TABLE 2. Prognosis of the patients with anterior skull base and craniofacial injuries

	SB	CF	SF	Total
Good	30	106	6	142
Poor	15	12	3	30
Dead	24	6	2	32
Total	69	124	11	204

SB, anterior skull base injury; CF, craniofacial injury; SC, anterior skull base and craniofacial injury.

2 Materials

Two hundreds and four cases with anterior skull base and/or craniofacial injuries were encountered between 1997 and 2004. These cases included 169 men and 35 women, with an average age of 38.9 years. The patients were divided into three groups by way of injury, that is, Group SB (anterior skull base injury; 69 cases), Group CF (craniofacial injury; 124 cases), and Group SC (anterior skull base and craniofacial injury; 11 cases).

3 Results and Discussion

Cause of trauma was shown in Table 1. Traffic accident was most frequent, and included 114 cases. And fall, fight and others included 63, 18, and 9, respectively.

Prognosis of the patients was classified into good (good recovery or moderate disability), poor (severe disabled or vegetative state) and dead according to Glasgow outcome scale at 3 month later (Table 2). In total 204 patients, about 70% (142 cases) included good outcome. Fifteen percent (30 cases) and 16% (32 cases) included poor and dead outcome, respectively. In the patients with anterior skull base injury, the number of the patients with dead outcome was extremely higher (37.8%) than those with craniofacial (4.8%) and/or anterior skull base and craniofacial (18.2%) injury. In the patients with craniofacial injury, their prognosis indicated the good trend.

Mean Glasgow coma scale [4] on admission was 8.7 in the patients with anterior skull base injury, 12.6 in craniofacial injury, and 10.6 in anterior skull base and cran-

TABLE 3. Mean Glasgow Coma Scale (GCS) on admission in the patients anterior skull base and craniofacial injuries

	SB	CF	SF
Mean GCS	8.7	12.6	10.6
Good	12.3	13.6	12.7
Poor	7.7	7.3	8.7
Dead	3.8	4.8	4.5

SB, anterior skull base injury; CF, craniofacial injury; SC, anterior skull base and craniofacial injury.

TABLE 4. Summary of treatment in the patients anterior skull base and craniofacial injuries

	SB	CF	SC	Total
Conservative	44	62	5	111
Surgery	25	62	6	91
Total	69	124	11	204

SB, anterior skull base injury; CF, craniofacial injury; SC, anterior skull base and craniofacial injury.

iofacial injury (Table 3). In each group, the patients with good outcome had a tendency to be good consciousness on admission. On the other hand, in the patients with bad outcome, mean GCS had low trend. Mean GCS on admission and prognosis had a tendency to be similar in each group.

Summary of treatment was shown in Table 4. Conservative therapy was performed in 111 cases. Surgical treatment had done in 93 cases (25 on anterior skull base injury, 62 on craniofacial injury, and 6 on anterior skull base and craniofacial injury).

And, relationship between prognosis and treatment was analyzed in each group.

3.1 (1) Anterior Skull Base Injury (69 Cases, Mean GCS 8.7)

In this group, 30 cases had good prognosis, and their mean GCS on admission was 12.3. Conservative therapy was performed in 25 patients, and surgery was done in 5 cases. In surgery group, 2 patients had reconstruction of the anterior skull base, one had embolization for traumatic carotid cavernous fistula, and 3 had intracranial pressure monitoring and/or ventricle drainage.

Patients with poor outcome had 15 cases, and their mean GCS was 7.7. Conservative therapy was performed in 15 cases, and surgery was done in 7 cases. Of 7 cases, 4 patients had external decompression, 2 had ICP monitoring, and one had hypothermia.

Patients with dead outcome had 24, and their mean GCS was 3.8. Of 24 cases, 11 had conservative therapy, and 13 had surgical treatment. In surgical treatment, removal of hematoma was performed in 6 cases, ligation of external carotid artery and intracranial pressure monitoring were done in 4 and 3 patients, respectively. Ligation of external carotid artery was effective for massive nasal bleeding, but patient

could not be alive because of severe brain damage. In this group, the main cause of death was direct brain damage.

3.2 (2) Craniofacial Injury (124 Cases, Mean GCS 12.6)

Of the 124 cases, 106 cases had good outcome, and their mean GCS was 13.6. Conservative therapy was performed in 54 cases, and surgery was done in 52 cases. All of the patients with surgery had open reduction and internal fixation, and which was performed by plastic surgeons.

Twelve cases had poor outcome, and their mean GCS was 7.3. Three patients had conservative therapy, and 9 had surgical treatment. Open reduction and internal fixation was done in 6 cases and one of them was simultaneously performed the decompression of optic canal. On the other hand, removal of hematoma and hypothermia were performed in 2 and one case, respectively.

Six cases died of craniofacial injury, and their mean GCS was 4.8. Surgical treatment could not be done in five patients because of bad general condition by multiple injury. One patient had ligation of external carotid artery. This was successful, but he died of severe brain damage. The main cause of death in this group was multiple injury or severe brain damage.

3.3 (3) Anterior Skull Base and Craniofacial Injury (11 Cases, Mean GCS 10.6)

Six cases had good outcome, and their mean GCS was 12.7. Conservative therapy was done in one patient, and surgery was done in 5 cases. Of the 5 cases, 3 had open reduction and internal fixation; one had ligation of external carotid artery and made a good recovery in spite of massive nasal bleeding with hemorrhagic shock. And other one patient had reconstruction of the anterior skull base.

Three patients had poor outcome, and their mean GCS was 8.7. Two cases had no surgery, and one had embolization of the maxillary artery for massive nasal bleeding.

Two patients had died of multiple multiple injury or severe meningitis. GCS on admission of one patient was 3, and he died of multiple injury. Other patient's GCS was 6. He survived for several weeks after injury but died of severe meningitis.

4 Conclusion

During past 8 years, we have encountered 204 cases of the anterior skull base and craniofacial injuries.

In the patients with anterior skull base injury, their conscious level on admission was bad (mean GCS was 8.7). Poor or dead cases exceeded 50%. And one patient could not be alive because of severe meningitis in spite of our intensive care.

In the patients with craniofacial injury, their conscious level on admission was good (mean GCS was 12.6). Over 85% of the patients had good recovery. And one patient with anterior skull base and craniofacial injury, who had less severe brain damage, died of severe meningitis with uncontrollable cerebrospinal fluid leakage.

As to embolization or ligation of the external carotid artery, they seemed to be effective in the patients with good conscious level on admission, but less effective in the patients with bad conscious level because of severe brain damage and/or multiple injury.

On the other hand, 2 patients died of severe meningitis because of uncontrollable cerebrospinal fluid (CSF) leakage in spite of our intensive care. So, it is suggested that even greater careful management should be done for CSF leakage.

References

1. Clauser L, Dallera V, Sarti E, et al (2004) Frontobasilar fractures in children. Childs Nerv Syst 20:168–175
2. Rocchi G, Caroli E, Belli E, et al (2005) Severe craniofacial fractures with frontobasal involvement and cerebrospinal fluid fistula: Indications for surgical repair. Surg Neurol 63:559–563
3. Samii M, Tagagiba M (2002) Skull base trauma: diagnosis and management. Neurol Res 24:147–156
4. Teasdale G, Jennett B (1974) Assessment of coma and impaired consciousness: A practical scale. Lanset II:81–84

Oxidative Injury and Antioxidant Therapy in Acute Brain Injury

YUKIO IKEDA

Summary. A large body of evidence suggests that oxidative injury is important in either the primary or downstream secondary pathophysiological mechanisms underlying acute traumatic and ischemic brain injuries. Measurement methods of oxidative stress are performed by electron spin resonance (ESR) which is one of the most reliable methods for detection and generation of oxygen free radicals in vitro and in vivo. Experimental investigations have reported that early administration of free radical scavengers can promote survival and neurological recovery. Edaravone, a novel free radical scavenger, is available clinically for cerebral infarction, which may be feasible to use for traumatic brain injury.

Key words. free radicals, brain injury, electron spin resonance spectroscopy, Edaravone, brain protection

Oxygen free radicals have been implicated in the genesis of acute brain injury and brain edema [1–3]. Oxidative stress—induced brain damage is critical for understanding mechanisms of brain diseases. This paper will discuss oxidative injury and antioxidant therapy in acute brain injury.

1 Role of Oxygen Free Radicals

1.1 Production of Oxygen Free Radicals in Traumatic Brain Injury

Experimental traumatic brain injury (cryogenic brain injury) was produced by application of a metal probe cooled with dry ice to the dura of the right parietal region in male Wistar rats and cats. Detection of superoxide radicals was performed by nitro-

Department of Neurosurgery, Tokyo Medical University Hachioji Medical Center, 1163 Tatemachi, Hachioji, Tokyo 193-0998, Japan

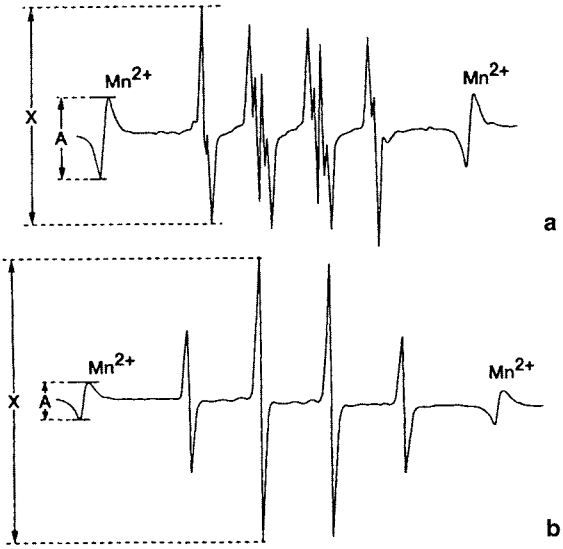


FIG. 1. Determination of (a) superoxide radical and (b) hydroxyl radical scavenging activity by electron spin resonance spectrometry (ESR) using the spin trap method. Relative signal intensity = X/A. *X*, signal intensity; *A*, marker intensity

blue tetrazolium (NBT) method by a cranial bone window technique [4]. Cryogenic brain injury demonstrated overproduction of superoxide radicals which was shown by the deposition of reduced NBT in the injured parietal region [5].

1.2 Consumption of Endogenous Free Radical Scavenging Activity

Increased formation of oxygen free radicals may lead to a consumption of endogenous free radical scavenging activity. Determination of endogenous sueperoxide scavenging activity in the injured brain was performed by electron spin resonance spectrometry (ESR) using DMPO (5,5-dimethyl-1-pyrroline-N-oxide) as a spin trapping agent (Fig. 1). Superoxide scavenging activity was significantly decreased within one hour after the cryogenic brain injury relative to non-injured brain, persisting for at least 6 hours (Fig. 2) [6].

Endogenous free radical scavenger system may be an early target for traumatic brain injury.

2 Experimental Antioxidant Therapy

2.1 Superoxide Dismutase (SOD)

Free SOD did not reduce cryogenic brain edema and BBB disruption, however liposome—entrapped SOD dramatically reduced cryogenic brain edema and BBB disruption [7,8], which indicated that oxygen free radicals may be involved in the genesis of traumatic brain injury and brain edema and exogenous administration of free radical scavenger will be a therapeutic potential for acute brain injury and brain edema.

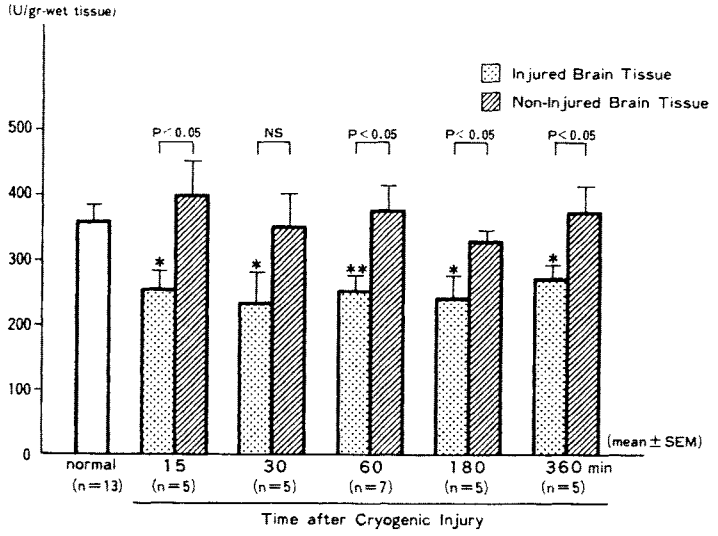


FIG. 2. Superoxide scavenging activities in cryogenic injured brain tissues (from reference [6]). $^{*}P < 0.05$ *vs* normal, $^{**}P < 0.01$ *vs* normal

2.2 Deferoxamine

Among oxygen free radicals, the hydroxyl radical is one of the most highly reactive species. The hydroxyl radical reacts at great speed with almost every molecule found in living cells, including DNA, proteins and also attacks the fatty acid chains and starts the process of lipid peroxidation. Hydroxyl radicals is produced from two active oxygen species, superoxide and hydrogen peroxide, via the iron-catalyzed Haber–Weiss reaction. From the therapeutic standpoint, iron chelation could inhibit the formation of hydroxyl radicals and potentially reduce brain injury and brain edema.

We have demonstrated that deferoxamine, an iron chelating agent, could scavenge hydroxyl radical, which was determined by ESR using DMPO as a spin trapping agent (Fig. 1). We also have reported neuroprotective effect of deferoxamine on cryogenic brain injury and brain edema in cats in Journal of Neurosurgery in 1989. Brain edema was evaluated by specific gravity method and blood brain barrier (BBB) disruption was measured by Evans blue extravasation. Deferoxamine reduced cryogenic-induced brain edema and BBB disruption (Fig. 3) [9].

Exogenous administration of free radical scavenger may be considered as a effective therapeutic approach in clinical situation.

3 Clinical Antioxidant Therapy and Edaravone

Most recent clinical trials on neuroprotection for traumatic brain injury and brain edema in United Staes of America have failed [10]. Only free radical scavenger and brain hypothermia seem to be promising for the treatment of acute brain injury and brain edema.

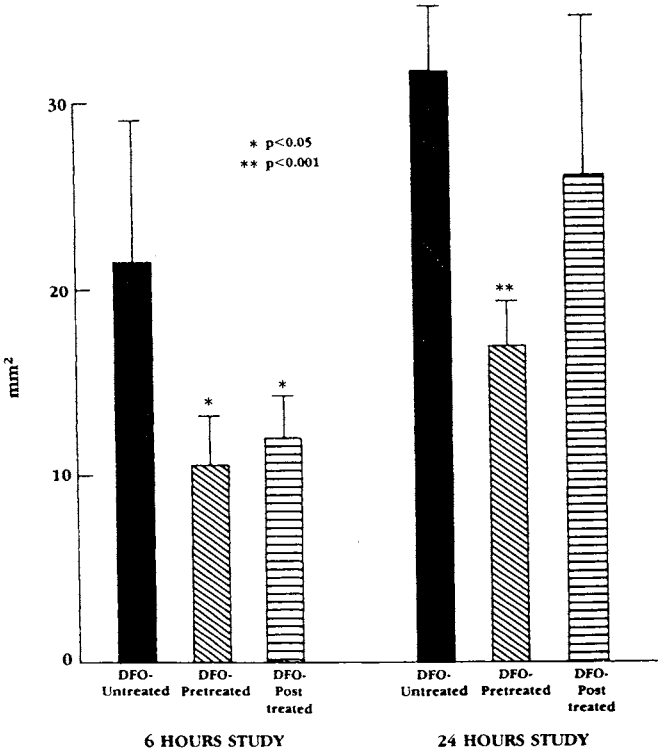


FIG. 3. Effect of deferoxamine on BBB (blood brain barrier) disruption (from reference [9]). Histogram showing the area of Evans blue dye extravasation. Data are presented as means ± standard deviations. *Asterisks* indicate a significant difference from the untreated group. *DFO*, deferoxamine

A novel free radical scavenger is coming up in Japan. Edaravone, a novel free radical scavnegr, demonstrates neuroprotective effects by inhibiting endothelial cellular injury and ameliorating neuronal damages in experimental ischemic brain models [11]. Recent clinical trials have demonstrated that Edaravone is effective for the treatment of acute brain infarction. Within 24h after cerebral infarction, Edaravone improved neurological functions and mortality [12]. Edaravone is the only available free radical scavenger in clinical practice for stroke in Japan.

Edaravone may be feasible to use for the treatment of traumatic brain injury and brain edema.

3.1 *In vitro ESR Study of Edaravone*

ESR technique is recognized as one of the most powerful methods for the detection of the generation of oxygen free radicals in biological system. In vitro X-band ESR system is useful for direct detection of oxygen free radicals.

Hydroxyl radical scavenging activity was measured by ESR using DMPO as a spin trapping agent. Edaravone can scavenge hydroxyl radicals in a dose dependent

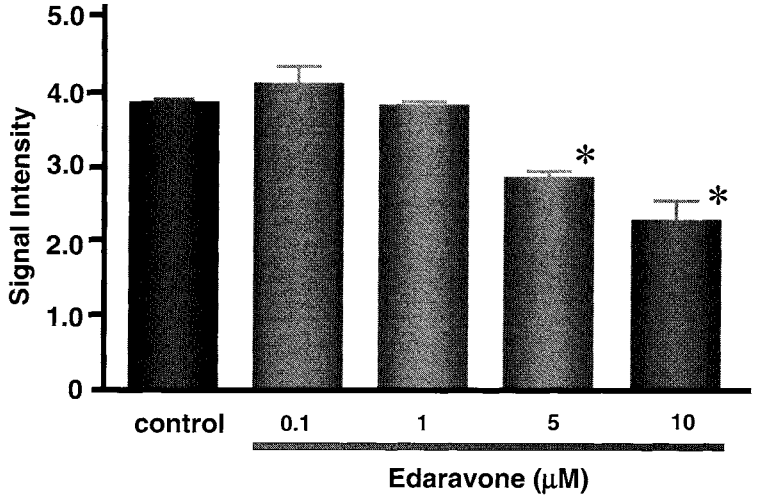


FIG. 4. Hydroxyl radical scavenging activity of Edaravone

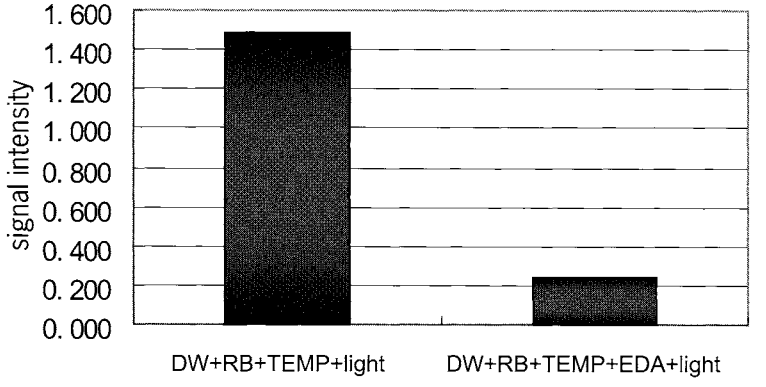


FIG. 5. Singlet oxygen scavenging activity of Edaravone. *DW*, distilled water; *RB*, rose bengal; *TEMP*, tetramethylpiperidine; *EDA*, edaravone; *light* (illumination 6,000 lux)

manner (Fig. 4). Singlet oxygen scavenging activity of Edaravone was determined by ESR with spin trap method. Singlet oxygen was generated by photoexcitation of the light-sensitive dye rose bengal. 2,2,6,6-tetramethylpipridine (TEMP) was used as the spin trapping agent. Edaravone can also scavenge singlet oxygen (Fig. 5). Nitric oxide (NO) scavenging activity was perfomed by ESR with the spin trap method. NO was generated from 1—hydroxyl—2oxo—3—(N—3—methyl—3—aminopropyl)—3—methyl—1—triazene (NOC—7), and analyzed by 2—(4—carboxy—pheny) 4,4,5,5—tetramethylimidazoline—1—oxy (carboxy—PTI) produced from the reaction between carboxy—PTIO and NO. Satoh et al. reported in REDOX REPORT in 2002 that Edaravone can also scavenge NO radicals [13].

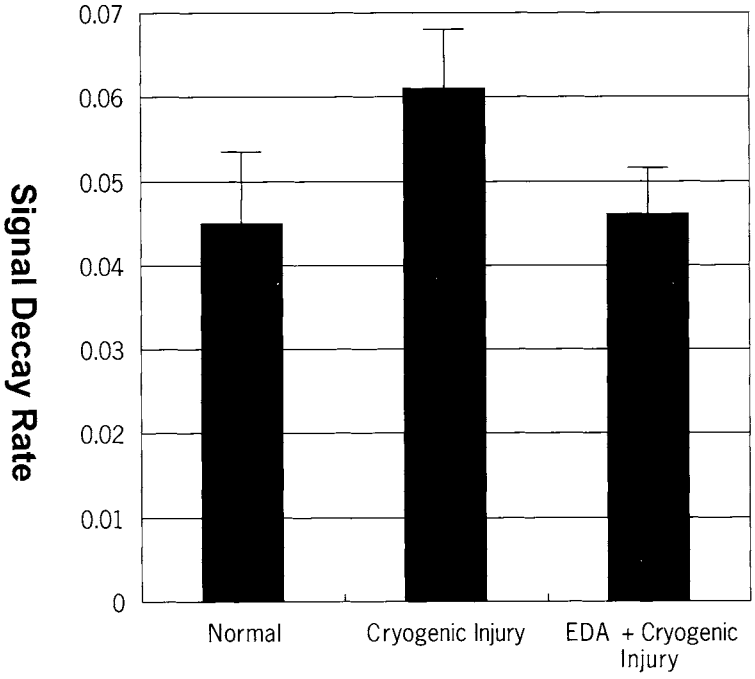


FIG. 6. L-band ESR signal decay constant of MC-PROXYL in the head region of live rats by Edaravone

3.2 *In vivo ESR Study of Edaravone*

In vivo L—band ESR is also useful for investigation of reaction with oxygen free radicals in living animals non—invasively [14,15]. Nitroxyl radicals are very useful as exogenous spin probes for measuring free radical distribution, oxygen concentration, and redox metabolism by in vivo ESR biological systems. MC—PROXYL is suitable spin probe for the study of free radical reactions in the brain by in vivo ESR detection. MC—PROXYL is more lipophilic with high permeability of BBB and is well distributed in the brain [16]. The nitroxide radicals loses its paramagnetism by interaction with oxygen free radicals and ESR spectra will decrease. The enhanced signal decay is closely related to amounts of oxygen free radicals. L—band ESR signal decay rate of MC—PROXYL in the head region of normal, cryogenic brain injury, and cryogenic brain injury with Edaravone administered after intravenous injection of MC—PROXYL were investigated in male Wistar rats. The decay rate of MC—PROXYL was faster in rats with cryogenic brain injury than in normal rats. The decay rates of MC—PROXYL was slower in rats with Edaravone treated cryogenic brain injury than in rats with cryogenic brain injury (Fig. 6). Acutually Edaravone can scavenge oxygen free radicals in the live brain.

Edaravone is expected to be useful in the treatment of acute brain injury and brain edema, demonstrated by in vitro and in vivo ESR studies.

References

1. Ikeda Y, Long DM (1990) Review article. The molecular basis of brain injury and brain edema: The role of oxygen free radicals. Neurosurgery 27:1–11
2. Gilgun-Sherki Y, Rosenbaum Z, Melamed E, et al (2002) Antioxidant therapy in acute central nervous system injury: Current state. Pharmacol Rev 54:271–284
3. Lewen A, Matz P, Chan PH (2000) Free radical pathways in CNS injury. J Neurotrauma 17:871–890
4. Kontos HA (1986) Superoxide production in experimental brain injury. J Neurosurg 64:803–807
5. Ikeda Y, Anderson JH, Long DM (1989) Oxygen free radicals in the genesis of traumatic and peritumoral brain edema. Neurosurgery 24:769–785
6. Ikeda Y, Toda S, Wang M, et al (1994) Early changes of blood-brain barrier and superoxide scavenging activity in rat cryogenic brain injury. Acta Neurochir Suppl 60:136–138
7. Chan PH, Longar S, Fishman RA (1987) Protective effects of liposome-entrapped superoxide dismutase on posttraumatic brain edema. Ann Neurol 21:540–547
8. IkedaY, Brelsford KL, Ikeda K, et al (1990) Effect of superoxide dismutase in cats with cold-induced edema. Adv Neurol 52:203–210
9. Ikeda Y, Ikeda K, Long DM (1989) Protective effect of the iron chelator deferoxamine on cold-induced brain edema. J Neurosurg 71:233–238
10. Doppenberg EMR, BullockR (1997) Clinical neuroprotection trials in severe traumatic brain injury: Lessons from previous studies. J Neurotrauma 14:71–80
11. Abe K, Yuki S, Kogure K (1988) Strong attenuation of ischemic and postischemic brain edema in rats by a novel free radical scavenger. Stroke 19:480–485
12. Edaravone Acute Infarction Study Group (2002) Effect of a novel free radical scavenger, edaravone (MCL-186), on acute brain infarction. Cerebrovasc Dis 15:222–229
13. Satoh K, Ikeda Y, Shioda S, et al (2002) Edaravone scavenges nitric oxide. Redox Rep 7:219–222
14. Yamamoto M, Egashira T, Utsumi H (2003) Application of in vivo ESR spectroscopy to measurement of cerebrovascular ROS generation in stroke. Free Radic Biol Med 35:1619–1631
15. Nakamura H, Sekino H (2002) Free radical reaction and effects of edaravone on experimental brain injury. St. Marianna Med J 30:379–387
16. Lee MC, Shoji H, Miyazaki H, et al (2004) Assessment of oxidative stress in the spontaneously hypertensive rat brain using electron spin resonance (ESR) imaging and in vivo L-band ESR. Hypertens Res 27:485–492

The Development of Brain Hypothermia Treatment for Severe Brain Trauma: New Finding of Brain Injury Mechanism, ICU Management Technique and Pitfall

NARIYUKI HAYASHI

Summary. For long time, we have been misunderstanding the management target for brain resuscitation. Recent clinical studies in severe brain injured patient, demonstrated patient specific new brain injury mechanism associated with hypothalamus-pituitary adrenal axis activated neurons-hormonal reactions. The elevation of brain tissue temperature (>40°C) by brain thermo-pooling, neuronal hypoxia by hemoglobin dysfunction even with normal control of PaO2, CBF, ICP, and oxygen delivery are included as new finding brain injury mechanisms. The previous management method such as control of ICP, CBF, and brain edema is not effective for all of these new finding brain injury mechanisms. The selective radical damage of dopamine A 10 nervous system bring to persistent vegetative state is also another new topics. The new concept of brain hypothermia treatment has progressed with understanding of these new finding brain injury mechanisms. The control of brain tissue temperature, precise care management for oxygen and glucose metabolism in the brain tissue, and early preventative treatment for radical attack to the dopamine nervous system is especially important for severe brain damage. We appreciate excellent clinical results in severe brain trauma patients using this brain hypothermia treatment.

Key words. brain hypothermia, severe brain injury, complication of hypothermia, hemoglobin dysfunction, free radicals

1 Introduction

The effectiveness of neuroprotection to the ischemic brain insults by brain hypothermia in animal studies is no doubt [1,2]. However, in clinical studies, similar effects of hypothermia were not obtained like animal studies in previously [3]. The reason of these different results is very simple "previous hypothermia management method has not been found human specific brain injury mechanism [4,5]. In this paper, I want present the new finding of patient specific brain injury mechanism [6,7] and

Advanced Research Institute of Science and Humanities, Nihon University, 6F Ichigaya Tokyu Building, 4-2-1, Kudan-Kita, Tokyo 102-0073, Japan

developed new brain hypothermia treatment method. The care management strategy for new finding brain damage, technique for control of brain tissue hypothermia, pitfall on the management of hypothermia, control of immune suppression and pneumonia [4,5], and early treatment for prevent of memory and emotional disturbances [4,8] are focused on in this paper.

2 New Finding of Brain Injury Mechanism on the Severely Brain Injured Patient

Our clinical studies about severe brain injured patients, hypothalamus-pituitary adrenal (HPA) axis neuro-hormonal brain injury mechanism has been evaluated [4,7,9]. These brain injury mechanisms, only recorded in severe brain injured patients, and not recorded in experimental animal brain injury models. Because, in experimental animal model, HPA axis stress reaction is reduce by anesthesia. The cardiopulmonary dysfunction by catecholamine surge [4], elevation of brain tissue temperature 40–44°C by brain thermo-pooling [4,6], increasing brain tissue lactate by insulin resisted hyperglycemia [4,5], masking neuronal hypoxia [5,7] and changes of blood brain barrier (BBB) function by vasopressin release [4] are find out on clinical studies. The masking neuronal hypoxia by difficulty release of oxygen from binding hemoglobin with reduction of hemoglobin 2,3 diphosphoglycerate (DPG) is, especially, important factor for decide the prognosis, directly. The normal control of PaO2, oxygen delivery, intracranial pressure (ICP) and CBF [9] is not effective for all of these patient specific brain injury mechanisms. The selective radical damage of dopamine A 10 nervous system is also another new topics as a cause of memory and emotional disturbances [8]. For long time, memory and emotional disturbances have been considered to be occurs with non-specific localized severe brain damage. However, our clinical studies demonstrated, simultaneous localized disturbances of hippocampus and amygdale nucleus in A10 central nervous system produces of high incidence of vegetate state conditions [8]. The $OH^{\cdot}$ radicals attacks that is produced by reacting with released dopamine and tissue oxygen [10] has been considered.

3 Management Strategy

The stabilizing the vital signs and brain oxygenation is initial treatment. However, before to start the management of brain edema, ICP elevation, and CBF disturbance, excess reaction of HPA axis-neurohormonal reaction should be control [4,5]. Insulin resisted hyperglycemia, hemoglobin dysfunction, ischemic cardiac muscle contraction, and brain thermo-pooling associated with catecholamine surge make an acceleration of worsening of brain damage at within a few minutes. Avoiding of selective neuronal radical damage of dopamine A 10 nervous system under the control of 32–34°C of brain tissue temperature and combined with replacement of serum albumin at higher than 3.0–3.5 g/dl are also effective for preventing persistent vegetation. As a third step ICU management, normal control of CBF, ICP, BBB, and

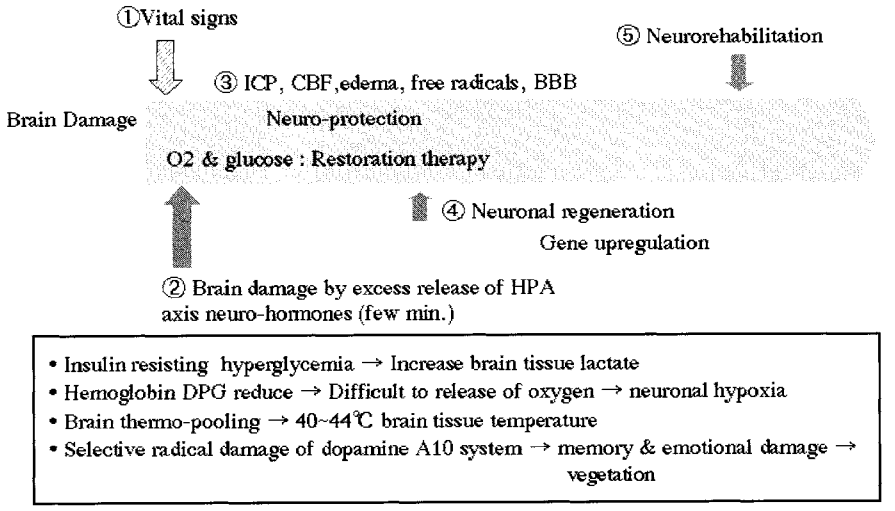


FIG. 1. Management strategy for severe brain damage. *HPA*, hypothalamus pituitary adrenal

preventing of brain edema are followed after these care management. The outline of management strategy for severe brain injured patients is summarized in Fig 1.

4 Management of Brain Damage by Excess Release of HPA-axis Neurohormones

The neuronal damage by catecholamine surge, insulin resisting hyperglycemia, and difficulty release of oxygen from binding hemoglobin with reduction of hemoglobin 2,3 DPG, unstable CBF by cardio-muscle contraction heart ischemia, higher than 40°C brain tissue temperature by brain thermo-pooling, and reducing thyroid hormone progress within at 10 min after brain injury associated with HPA-axis neurohormonal reaction [4,5,8]. Without early management for these brain injury mechanisms, brain hypothermia treatment is unsuccessful. The early induction of 34°C brain hypothermia with control of systemic circulation (cardiac index >500 ml/min.), serum glucose 120–140 mg/dl, serum albumin >3.0 g/dl, serum pH >7.2, antithrombin-III >130%, and replacement of magnesium and phosphate are main treatment for excess release of HPA axis neurohormones. Administration of steroid during stress associated hyperglycemia and manitol for anti-edema dehydration therapy is contraindicate during presence of HPA-axis neurohormonal reaction. The early induction of ~34°C brain hypothermia and then control the serum glucose at 120–140 mg/dl is especially important point for avoiding hypothermia induction pitfall. If persistent vegetation is expected to occur, after that, much lower 32–34°C moderate brain hypothermia is recommended.

5 Advanced Technique and Avoiding Pitfall on the ICU Brain Hypothermia Management

Most difficult point for this brain hypothermia treatment is precise control of brain tissue temperature, control of oxygen metabolism and insulin resisting hyperglycemia, management of pulmonary infections with an avoidable immune dysfunction, preconditioning of rewarming, and management of pitfall of hypothermia.

(1) Precise control of brain tissue temperature: The controlled brain hypothermia could be produce by cooling of systemic circulating blood temperature using blanket technique or intravascular cooling technique [4]. We prefer the combination brain cooling techniques with 7% iced acetic ringer solution drip and cooling suit technique (Fig. 2). As a strategy of brain cooling, ~34°C of brain tissue hypothermia or two steps induction of 32–34°C brain hypothermia treatment is recommended. Without control of hyperglycemia at 34°C brain hypothermia, hypothermia itself produces the increasing of brain tissue glucose and lactate, and also, activation of neural hypoxia by reducing hemoglobin DPG. This point is one of the pitfall of hypothermia management. Avoiding hyperglycemia higher than 180 mg/dl, cardio-pulmonary dysfunction such as arrhythmia and elongation of QT interval >450 mm/s on ECG, and hypokalemia are management care points at induction stage.

(2) Control of oxygen metabolism and insulin resisting hyperglycemia: Stabilizing vital signs, PaO2 >100 mmHg, PaO2/FiO2 ratio >350, PaCO2; 34–38 mmHg, oxygen delivery >700 ml/min., and oxygen extraction ratio (O_2ER); 22–26%, are essential care management. Avoiding of serum pH <7.3, reduction of serum phosphate, magnesium, and vitamin A, massive blood transfusion more than 6,000 ml is also necessary for prevent of hemoglobin DPG reduction.

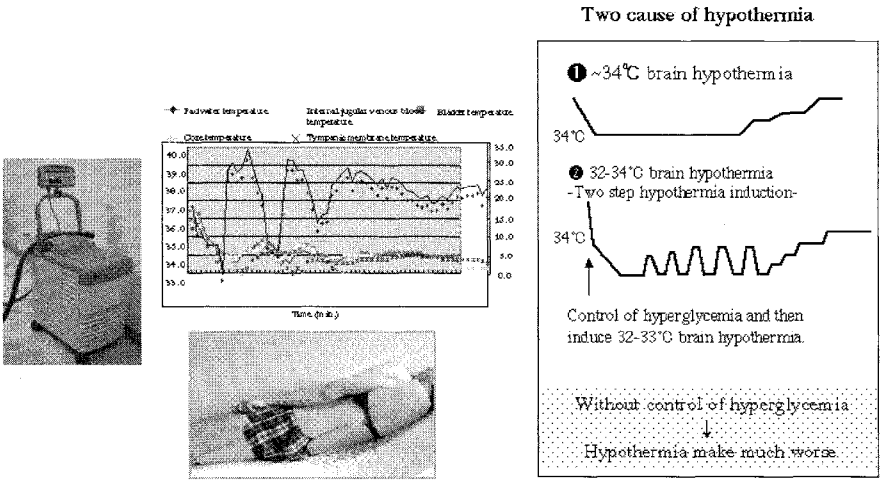


FIG. 2. Control of brain tissue hypothermia combined with 7% cold saline (sacsinate ringer solution) drip and automatic brain cooling technique (www.medivance.com, Louisville, CO. USA)

TABLE 1. Check list of respiratory care management during brain hypothermia treatment

Contents \ Check points	Care management
1. Ventilator	TV; 6 ml/kg, PEEP; 7 cmH_2O, Plateau P. ≥ 30 cmH_2O
2. Air way resistance (AWR)	$PaCO_2$; 25–40 mmHg, AWR < 10cmH_2O/L/SEC
3. Respiratory insufficiency	Abnormal breathing sounds, neck venous dilatation
4. Pulmonary circulation	systolic BP > 90 mmHg, ECG, edema of face and legs
5. Alveollar function	S. albumin > 2.5 g/dl, $ETCO_2/CO \cdot PaCO_2$): 0.1–0.2
6. Autonomic dysfunction	Unstable BP, changes of pulse during breathing pattern
7. Immune dysfunction	Feeble skeletal muscles, lymphocytopenia, growth hormone ↓
8. Intestinal bacterial translocation	Gastric juice pH < 3.5
9. Digestive organ function	Abdominal P. < 10 cmH_2O, AT-III > 100%, S. Alb. > 2.5 g/dl
10. Complication of pneumonia	Rales, deference of breathing sounds, sputum, fever
11. Pulmonary venous thrombosis	Reducing and difference of breathing sounds, edema of legs
12. Hemoglobin dysfunction	Serum pH > 7.3, serum glucose: 120–140 mg/dl

(3) Control of serum glucose: The reducing brain metabolism is not correct mechanism of brain hypothermia. Micro dialysis monitor in severe brain injured patients during brain hypothermia treatment suggested that precisely control of serum glucose are especially important for maintain the brain metabolism and avoiding BBB dysfunction [4,5].

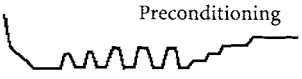
(4) Management of pulmonary infections with an avoidable immune dysfunction: The immune dysfunction is an avoidable by reducing growth hormone with hypothermia. Therefore, pulmonary infection occurs much easier than normothermia care management. Table 1 shows our checklist for respiratory organ management. Table 2 shows the summary of ICU management for immune crisis pulmonary infections. The patients own enterobacteria are souses of infection; therefore, enteral management is one of the key points.

(5) Preconditioning of rewarming: Avoiding hyperglycemia >180 mg/dl, hypoalbuminemia <3.0 g/dl, severe BBB dysfunction (CSF/serum albumin ratio >0.02), systemic infections is important. No evidence of neuronal recovery on CT, ICP, EEG, and jugular O_2 saturation is contraindication of rewarming.

6 Strategy for Management of Memory and Emotional Disturbances

The simple management for selective radical attack to the dopamine nervous system is prevention of dopamine release and control of NO radicals in acute stage. The early induction of brain hypothermia at 33–34°C is useful for prevent of dopamine release [4,6]. Pharmacological treatment, with metoclopramide also prevents the dopamine release from hypothalamus. Administration of radical scavengers is another approach for prevent of selective damage of dopamine A10 nervous system at the acute stage [8]. In severe brain injury cases, recovery of consciousness is not always enough after brain hypothermia treatment. The replacement of cerebral dopamine, the combination of pharmacological treatment such as Leodopa (300–400 mg/day), Amantadine

TABLE 2. The prevention of pneumonia during brain hypothermia treatment

The management target	Care management method
1. Intermittent brain tissue hypothermia	• Brain temperature Preconditioning 34°C 32°C 
2. Management for immune dysfunction	• Prolactin, arginine, metocloparamide, IGF-1, and growth hormone (GH) ad.
3. Management of hypo-albuminemia BBB dysfunction and hyperglycemia	• Serum albumin >3.0 g/dl, CSF/serum albumin < 0.01, serum glucose: 120–150 mg/dl
4. Maintain of systemic circulation	• Normovolemic fluid resuscitation and Doputamine (Dobutrex) iv
5. Good oxygenation	• DO_2 > 600 ml/min, DPG: 14–15 mmol/ml, S. phosphate > 3 mg/dl, S. magnesium: 2–4 mEq/dl
6. Gastric management and nutritional consideration	• Gastric lavage, gastric juice pH < 3.5, AT-III > 100%, Serum albumin > 3.0 g/dl, immunonutrition, digastric decontamination, and control of abdominal hypertension
7. Respiratory muscle care	• Glutamine, solbutamol, arginine ad. + respiratory rehabilitation

(100–200 mg × 3/day) or Parodel (2.5–20 mg/day), and administration of estrogen (Estraderm TTS 1 seat/day) is effective in chronic stage. The median nerve intermittent electrical stimulation (20 s-on, 50 s-off, 10–20 mA, 30 pulses/s., duration time 300 mm/s) are also effective [4,5,8]. The detail technique for management of memory and emotional disturbances is discussed at recent published book [4,8].

7 Clinical Result of Brain Hypothermia Treatment of Severe Brain Trauma

The brain hypothermia treatment was performed in 99 cases of severe brain injury GCS less than 6 and 36–37°C normothermia treatment was accepted for 64 cases of GCS less than 6. The efficacy of brain hypothermia was related to the severity of brain injury as indicated by the Glasgow Coma Scale on admission. The patients with initial coma scale of 3 did not benefit from brain hypothermia treatment, except cardiac arrested occur during surgery by uncontrollable massive hemorrhage with basal skull fracture. However, in GCS 4, 5 and 6, clinical benefit. Among these patients with higher scores, 29% in GCS 4, 26% in GCS 5, and 34% in GCS 6 in the brain hypothermia group had a good outcome. The normothermia group with previous concept treatment, good outcome is limited, 4% in GCS 4, 7% in GCS 5, and 6% in GCS 6, respectively. The effectiveness of brain hypothermia treatment for severe brain injured patients is impressive [4,5].

References

1. Busto R, Globus MY-T, Dietrich WD, et al (1989) Effect of mild hypothermia on ischemia-induced release of neurotransmitters and free fatty acids in rat brain. Stroke 20:904–910

2. Dietrich WD, Busto R, Halley M, et al (1990) The importance of brain temperature in alterations of the blood-brain barrier following cerebral ischemia. J Neuropathol Exp Neurol 49:486–497
3. Clifton GL, Miller ER, Choi SC, et al (2001) Lack of effect of induction of hypothermia after acute brain injury. N Engl J Med 344:556–563
4. Hayashi N (2004) Clinical management of brain hypothermia. In: Hayashi N, Dietrich DW (eds) Brain hypothermia treatment. Springer-Verlag, Tokyo, pp 37–325
5. Hayashi N (2004) A new concept of brain hypothermia treatment and pitfalls in intensive care units hypothermia management. In: Hayashi N, Bullock R, Dietrich DW, et al (eds) Hypothermia for acute brain damage. Springer-Verlag, Tokyo, pp 49–75
6. Hayashi N, Kinoshita K, Shibuya T (1997) The prevention of cerebral thermo-pooling, damage of A10 nervous system, and free radical reactions by control of brain tissue temperature in severely brain injured patients. In: Teelken A (ed.) Neurochemistry. Plenum Press, New York, pp 97–103
7. Hayashi N (2000) Enhanced neuronal damage in severely brain injured patients by hypothalamus, pituitary, and adrenal axis neuro-hormonal changes. In: Hayashi N (ed.) Brain hypothermia. Springer-Verlag, Tokyo, pp 3–26
8. Hayashi N, Mori T, Kinoshita K, et al (2004) Persistent vegetation means unconsciousness? How to manage vegetation and memory disturbances following severe brain damage. In: Hayashi N, Bullock R, Dietrich DW, et al (eds) Hypothermia for acute brain damage. Springer-Verlag, Tokyo, pp 327–342
9. Maclntosh TK (1994) Neurological sequele of traumatic brain injury: Therapeutic implications. Cerebrovasc Brain Metab Rev 6:109–162
10. Silvka A, Coben G (1985) Hydroxyl radical attack on dopamine. J Biol Chem 260:15466–15472

Hemodynamic Efficacy of Neuroleptanesthesia for Therapeutic Hypothermia in Acute Brain Injury

SHUNJI KASAOKA[1], YASUTAKA ODA[1], SUSUMU YAMASHITA[1], RYOSUKE TSURUTA[1], HIROSUKE FUJISAWA[2], KIYOSHI OKABAYASHI[1], and TSUYOSHI MAEKAWA[1]

Summary

Purpose: Therapeutic mild hypothermia (32–34°C) may act for cerebral protection. We examined the effects of anesthesia on hemodynamics during therapeutic hypothermia in human acute brain injury.

Methods: Eighteen patients with acute brain injury who had therapeutic hypothermia were retrospectively reviewed. The patients were divided into two groups by anesthesia: droperidol & fentanyl (NLA group), midazolam & butorphanol (MB group). Hemodynamic parameters during hypothermia were compared between the two groups.

Results: During the induction phase of mild hypothermia, hemodynamic parameters were not significantly different between the two groups. In the maintenance phase of mild hypothermia, cardiac index (CI), oxygen delivery index (DO_2I), and heart rate (HR) in NLA group were significantly higher than those in MB group. In NLA group, CI and DO_2I significantly increased in the maintenance phase from the induction phase of mild hypothermia. However, CI and DO_2I significantly decreased in MB group. HR did not significantly change in NLA group, however, it significantly decreased in MB group.

Conclusions: In comparison with anesthesia of midazolam and butorphanol, NLA might be superior in oxygen supply to general organs including brain and tissues, so that have less adverse effect to circulatory system.

Key words. therapeutic mild hypothermia, acute brain injury, neuroleptanesthesia, hemodynamics, cerebral protection

[1] Advanced Medical Emergency and Critical Care Center, Yamaguchi University Hospital, and [2] Department of Neurosurgery, Yamaguchi University School of Medicine, 1-1-1 Minami-Kogushi, Ube, Yamaguchi 755-8505, Japan

It has been reported that therapeutic mild hypothermia (32–34°C) may act for cerebral protection in acute severe brain injury [1–3]. To maintain body functions and to prevent any adverse effect from hypothermia, the patient should be well sedated and the microcirculation of organs and skin should be maintained [4]. We examined the effects of anesthesia on hemodynamics during therapeutic hypothermia in acute brain injury.

1 Methods

We have performed a retrospective review of 18 patients with acute brain injury who had therapeutic mild hypothermia. The patients were divided into two groups by anesthesia: droperidol & fentanyl (NLA group), and midazolam & butorphanol (MB group). To induce and maintain mild hypothermia, patients were cooled by a blanket and a mat with circulating cool water. The target core temperature was 32 to 34°C. To maintain microcirculation, colloid solution and/or dobutamine were used. We inserted a pulmonary artery catheter in all the patients and measured the hemodynamic parameters (Table 1) at induction phase and maintenance phase of therapeutic mild hypothermia. The doses of anesthetic agents in each group are shown in Table 2.

2 Results

In comparison of clinical characteristics of the patients, age and gender were not significantly different between the two groups. In the MB group, all patients had

TABLE 1. Hemodynamic parameters

- Mean arterial pressure (MAP)
- Heart rate (HR)
- Cardiac index (CI)
- Oxygen saturation of mixed venous blood (SvO_2)
- Systemic vascular resistance index (SVRI)
- Oxygen delivery index (DO_2I)

TABLE 2. The doses of anesthetic agents in each group

	MB group	NLA group
Droperidol		0.5 mg/kg (initial dose) 0.025 mg/kg/h
Fentanyl		5–10 μg/kg (initial dose) 0.02 mg/kg/day
Midazolam	0.1 mg/kg (initial dose) 0.1–0.2 mg/kg/h	If needed
Butorphanol	0.01 mg/kg (initial dose) 0.01–0.02 mg/kg/h	
Vecuronium	0.1 mg/kg (initial dose) 0.05 mg/kg/h	0.1 mg/kg (initial dose) 0.05 mg/kg/h

TABLE 3. Comparison of hemodynamic parameters in the maintenance phase of therapeutic hypothermia

	MB group	NLA group	*P* value
Hemoglobin (g/dl)	12.0 ± 1.3	10.9 ± 1.2	ns
Dobutamine (μg/kg/min)	3.9 ± 5.1	3.5 ± 1.9	ns
MAP (mmHg)	100 ± 14	101 ± 10	ns
HR (bpm)	60 ± 11	79 ± 6	<0.01
CI (l/min/m^2)	2.5 ± 0.5	3.7 ± 0.4	<0.01
SvO_2 (%)	79 ± 5	82 ± 2	ns
SVRI (dynes · sec · cm^{-5} · m^2)	3172 ± 833	2116 ± 239	<0.01
DO_2I (ml/min/m^2)	405 ± 66	557 ± 86	<0.01

Values are presented as mean ± standard deviation.
MAP, mean arterial pressure; HR, heart rate; CI, cardiac index; SvO_2, oxygen saturation of mixed venous blood; SVRI, systemic vascular resistance index; DO_2I, oxygen delivery index.

traumatic brain injury. On the other hand, in the NLA group, 6 patients had trauma and 2 patients had subarachnoid hemorrhage. Glasgow coma scale on admission and Glasgow outcome scale were not significantly different between the groups.

During the induction phase of mild hypothermia, hemodynamic parameters were not significantly different between the two groups. In the maintenance phase of mild hypothermia (Table 3), hemoglobin, dose of dobutamine and mean arterial pressure were not significantly different between the two groups, however, heart rate and cardiac index (CI) in the NLA group were significantly higher than those in the MB group. Systemic vascular resistance index (SVRI) was significantly lower and oxygen delivery index (DO_2I) was significantly higher in the NLA group.

In NLA group, CI and DO_2I significantly increased in the maintenance phase from the induction phase of mild hypothermia. However, CI and DO_2I significantly decreased in MB group. Heart rate (HR) did not significantly change in NLA group, however, it significantly decreased in MB group.

3 Discussion

Therapeutic mild hypothermia (32–34°C) may act for cerebral protection in acute severe brain injury. Sadamitsu et al [4] reported that to maintain body functions and to prevent any adverse effect from hypothermia, the patient should be well sedated, he should be prevented from shivering and the microcirculation of organs and skin should be maintained. We examined the effects of anesthesia on hemodynamics during therapeutic hypothermia in acute brain injury. Table 4 shows the summary of the effects of anesthesia on hemodynamics during hypothermia. In the MB group, heart rate, cardiac index and DO_2I decreased, and SVRI increased during hypothermia. On the other hand, in the NLA group, cardiac index, SvO_2 and DO_2I increased during hypothermia. We thought that the suppression of increase of systemic vascular resistance caused the better hemodynamic state in the NLA group. In spite of administration of dobutamine, heart rate and cardiac index decreased in MB group. We thought that dobutamine might be hard to work well during mild hypothermia by

TABLE 4. Effects of anesthesia on hemodynamics during therapeutic hypothermia

	MB group	NLA group
MAP	→	→
HR	↓	→
CI	↓	↑
SvO_2	→	↑
SVRI	↑	→
DO_2I	↓	↑

anesthesia of midazolam & butorphanol. In conclusion, compared with anesthesia of midazolam and butorphanol, NLA might be superior in oxygen supply to general organs and tissues, so that have less adverse effect to circulatory system.

References

1. Busto R, Deitolich WD, Glogus MY-T, et al (1989) Effect of mild hypothermia on ischemia-induced release of neurotransmitters and free fatty acids in rat brain. Stroke 20:904–910
2. The Hypothermia after Cardiac Arrest Study Group (2002) Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med 346:549–556
3. Bernard SA, Gray TW, Buist MD, et al (2002) Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. N Engl J Med 346:557–563
4. Sadamitsu D, Nakashima K, Maekawa T, et al (1996) Mild hypothermia with brain oriented intensive care for cerebral protection—Japanese experience. Bull Intensive Crit Care 3:11–14

Different Cytokine Responses between Induced and Accidental Hypothermia: An Implication for Controversies over Neuroeffective of Therapeutic Hypothermia

MAYUKI AIBIKI

Summary. In the clinical setting of induced hypothermia, cytokine responses or even neuroprotective effects remain controversial. This review shows differences in cytokine release between induced and accidental hypothermia, thereby trying to discuss potential mechanisms for controversies over the neuroprotection of induced hypothermia for TBI patients.

Key words. accidental hypothermia, cytokine, therapeutic hypothermia, traumatic brain injury

1 Introduction

It is established in the animal models that cerebral cytokine overproduction is involved the subsequent neuronal death after traumatic brain injury (TBI) [1,2]. Such cytokine surge after TBI could be inhibited by induced hypothermia in the animal, leading to improvement in the neurological outcome [1,2]. However, in the clinical setting of induced hypothermia, cytokine responses or even neuroprotective effects remain controversial. On the other, we have demonstrated that in accidental hypothermia even activated cytokine production occurs [3]. Objective of this review is to discuss potential mechanisms for controversies over the neuroprotection of induced hypothermia for TBI patients.

Department of Emergency Medicine, Ehime University, School of Medicine, Ehime, Japan

Correspondence: Mayuki Aibiki, M.D., Ph.D., Department of Emergency Medicine, Ehime University, School of Medicine, 454 Shitsukawa, Tohon, Ehime 791-0295, Japan

2 Controversies over Cytokine Changes during Hypothermic Therapy

2.1 Papers Showing Neuroprotective Effects and Simultaneous Cytokine Reduction in TBI Patients

Dr. Marion and colleagues demonstrated clearly that cerebro-spinal fluid inter-leukin 1β (CSF IL-1β) in TBI patients receiving hypothermia 32°C under administration of narcotics and vecuronium was significantly lower than those in normothermia [4]. In the paper, they also reported that neurological outcome of patients with GCS 5 to 7 on admission was superior in hypothermia than in normothermia groups. Another important point in the paper is that in the hypothermia group, vegetative patients were lesser than in normothermia group (the percentage of vegetative state: hypothermia group 8% *vs* normothermia 17%). They also showed that hypothermia for 24 h did not increase the rate of pneumonia.

We have reported that in TBI patients serum IL-6 levels increased and that such elevation was attenuated by hypothermia, suggesting anti-inflammatory effects of hypothermia [5]. We have also demonstrated in the paper that IL-6 levels in internal jugular plasma were much higher than those in systemic plasma in TBI patients, and internal jugular IL-6s were decreased by induced hypothermia under administration of midazolum, buprenorphine and vecuronium. This suggests that hypothermia might also attenuate cerebral cytokine production. Furthermore, we have found improvement in the neurological outcome in the hypothermia group as compared to normothermia group. There were no significant differences in the rate of pneumonia between the two groups.

2.2 Papers Demonstrating Ineffectiveness of Hypothermic Therapy on Outcome and Cytokine Release in TBI Patients

Dr. Shiozaki and colleagues reported that hypothermia 34°C induced by administration of barbiturates did not decrease CSF IL-1β elevation after TBI or even failed to find beneficial effects of the therapy on TBI patients with low intracranial pressure [6]. In the paper, it is also reported that CSF IL-1β elevated even in patients with low intracranial pressure. Careful reading for the paper leads us to find huge variations of the CSF IL-1β data as well as the limited number of patients.

In the series of their study, it is reported that hypothermia 34°C more than for 48 h did not improve neurological outcome in TBI patients with low intracranial pressure, and the percentage of vegetative patients were relatively high in hypothermia group [7]. More importantly, the percentage of pneumonia in the hypothermia group was much higher than those in normothermia group (the rate of pnemonia: hypothermia 49% *vs* normothermia 15%).

2.3 Hypotheses after Reviewing Controversial Issue

After reviewing the previous papers regarding cytokine production in TBI patients treated with hypothermic therapy [1–6], we could raise hypotheses for different

cytokine responses during induced hypothermia in humans as follows: (1) there might be temperature dependency in cytokine production and (2) systemic infection such as pneumonia might affect cerebral cytokine production.

2.4 Cytokine Changes in Accidental Hypothermia

We have reported that in patients with accidental hypothermia, IL-6 levels were high already on admission and on the rewarming period, such cytokine levels increased remarkably [3]. Dr. McInerney and colleagues demonstrated that tumor necrotic factor-α (TNF-α), the first runner among the cytokines, increased as the body temperature decreased [8]. Obviously, there were no anesthetics given in accidental hypothermia patients. Thus, it is likely that if no adequate administration of anesthetics, hypothermia could be enormous physiological stresses for humans. Thus, in humans, hypothermia *per se* might not suppress pro-inflammatory cytokine release. This might depend on (1) body temperature, (2) anesthetic level or (3) systemic responses.

2.5 Implication of the Present Review

Recently, systemic inflammatory responses have been shown to affect injured brain [9], suggesting that extra-cerebral insults might change the outcome of brain injury. Therefore, systemic inflammatory responses to certain physiological derangements during therapeutic hypothermia, such as hemodynamic depressions or systemic infection, might also modulate neuroprotective effects of hypothermia in TBI patients [10]. Thus, implication of this review is that during induced hypothermia in humans, if anesthetic level is not adequate, if systemic management including pulmonary infection control is not well done, cytokine responses could be modulated, which may lead to failure in obtaining the beneficial effects of hypothermic therapy.

References

1. Kinoshita K, Chatzipanteli K, Vitarbo E, et al (2002) Interleukin-1beta messenger ribonucleic acid and protein levels after fluid-percussion brain injury in rats: Importance of injury severity and brain temperature. Neurosurgery 51:195–203
2. Vitarbo EA, Chatzipanteli K, Kinoshita K, et al (2004) Tumor necrosis factor alpha expression and protein levels after fluid percussion injury in rats: The effect of injury severity and brain temperature. Neurosurgery 55:416–424
3. Aibiki M, Maekawa S, Nishiyama T, et al (1999) Activated cytokine production in patients with accidental hypothermia. Resuscitation 41:263–8
4. Marion DW, Penrod LE, Kelsey SF (1997) Treatment of traumatic brain injury with moderate hypothermia. N Engl J Med 336:540–546
5. Aibiki M, Maekawa S, Ogura S, et al (1999) Effect of moderate hypothermia on systemic and internal jugular plasma IL-6 levels after traumatic brain injury in humans. J Neurotrauma 16:225–232
6. Shiozaki T, Kato A, Taneda M, et al (1999) Little benefit from mild hypothermia therapy for severely head injured patients with low intracranial pressure. J Neurosurg 91:185–191
7. Shiozaki T, Hayakata T, Taneda M (2001) A multicenter prospective randomized controlled trial of the efficacy of mild hypothermia for severely head injured patients with

low intracranial pressure. Mild Hypothermia Study Group in Japan. J Neurosurg 94: 50–54
8. McInerney JJ, Breakell A, Madira W, et al (2002) Accidental hypothermia and active rewarming: The metabolic and inflammatory changes observed above and below 32°C. Emerg Med J 19:219–223
9. Hang CH, Shi JX, Tian J, et al (2004) Systemic inflammatory responses affect injured brain. Brain Res 1026:23–32
10. Aibiki M (2004) Practical aspects and prevention of complications during therapeutic hypothermia. Intensive Care Med 30:2286

Multidisciplinary Treatment Including Brain Hypothermia for Severe Brain Injury

Yoshio Takasato and Takanori Hayakawa

Summary. The clinical effect of the brain hypothermia treatment was denied with RCT study of the severe brain injury in U.S.A. at 2001 report. It is not necessary to deny all of them under the lack condition of other clinically effective brain protection treatment. It is meaningful to examine in which part the hypothermia therapy is effective and to re-examine the treatment indication. We have analyzed comparatively the brain hypothermia therapy and conventional neurotrauma treatment in our institutional data and the Japan Neurotrauma Data Bank data to inspect whether our institutional result which is relatively small sample analysis is universal or not. We obtained the almost same result in both analyses. The effect of hypothermia therapy was high in the severely injured group. In other words, it was suspected that the group predicted of bad outcome in the non-hypothermia treatment was good indication of the hypohtermia therapy. It was suspected that positive expansion of indication for the hypothermia therapy in younger age group and limit of all multidisciplinary treatment in severe brain injury.

We have analyzed and have compared the brain hypothermia treatment and conventional neurotrauma treatment until now [1,2]. Secondary, we analyzed the Japan Neurotrauma Data Bank data to inspect whether our institutional result which is relatively small sample analysis is universal or not.

Department of Neurosurgery, National Hospital Organization Disaster Medical Center, 3256 Midori-cho, Tachikawa, Tokyo 190-0014, Japan and The Japan Neurotrauma Data Bank Committee, Japan

1 First Stage Analysis: Change of Prognostic Clinical Indicators of Severe Brain Injury Treated by Brain Hypothermia

1.1 Introduction

Brain hypothermia treatment has two aspects of nature of efficacy and side effects. Although the efficacy for the brain injury is demonstrated experimentally [3], the efficacy is denied for the clinical result in the present condition [4]. We examined the role and problem of the mild brain hypothermia in neuro-intensive care of the severe brain injury. Especially, factors that correlated to the poor outcome were analyzed.

1.2 Materials

Object were severe brain injury patients who's Glasgow Coma Scale(GCS) on admission were 8 or less. Acute subdural hematoma(ASDH), acute brain swelling «Traumatic Coma Data Bank(TCDB)—CT classification Diffuse injury III & IV», cerebral contusion and traumatic intracerebral hematoma were included. Twenty-one early period patients (A group) were treated by neuro-intensive care other than the brain hypothermia. Forty-three later period patients (B group) were treated with additional brain hypothermia.

1.3 Methods

The cooling was carried out with The whole body water cooling by the blankets. The temperature was controlled with jugular bulb blood temperature. The target temperature of the cooling was made at 32–35°C. After this temperature setting for 3 days, the patient was rewarmed gradually to 37°C during next 4 days. The outcome was evaluated by Glasgow Outcome Scale (GOS) on discharge (Table 1).

1.4 Results

The comparatively better outcome was obtained with the B group. The rate of good outcome (GR/MD) and that of death were 9%, 81% in the A group and 21%, 37% in

TABLE 1. Characteristics of patients

	A group: 21	B group: 43
Mean age	50.4 ± 9.3	40.3 ± 7.4
Male/Female	15/6	32/11
Main disorder	ASDH 14	ASDH 29
	Contusion 3	Contusion 8
	Swelling 4	Swelling 6
GCS (on admission)	3.9 ± 1.2	4.7 ± 1.3
Mortality (%)	81	37
GOS (on discharge)	2.8 ± 2.7	3.4 ± 1.6
GR-MD (%)	9	21

the B group respectively. GCS on admission, pupil size, blood pressure (shock level), light reflexes and effacement of the basal cistern in CT on admission showed the strong correlation with outcome (GOS) in the former. It was not so in the latter.

1.5 Conclusions

There are various many brain protection mechanisms in the brain hypothermia treatment. If we can control the side effect of the brain hypothermia while using these brain protection mechanisms well, the clinical effect that resembles the experimental result might be able to expect. In our study, the most severe brain injury patients were not possible to rescue in the conventional treatment without brain hypothermia. The recovery and neuro-protective mechanism by brain hypothermia is different from the conventional one.

2 Second Stage Analysis: Analyzed Result of the Japan Neurotrauma Data Bank (JNTDB) Data

Object were severe brain injury patients who's Glasgow Coma Scale (GCS) on admission were 8 or less. Acute subdural hematoma(ASDH), acute brain swelling «Traumatic Coma Data Bank (TCDB)—CT classification Diffuse injury III & IV», cerebral contusion and traumatic intracerebral hematoma were included. Five hundreds seventy nine patients (Non-hypothermia group) were treated by neuro-intensive care other than the brain hypothermia. One hundred twenty nine patients (Hypothemia group) were treated with additional brain hypothermia. The outcome was evaluated by Glasgow Outcome Scale (GOS) on discharge and final GOS (6–12 months) (Tables 2,3 and Fig. 1).

2.1 Results (Table 4)

(1) Brain hypothermia treatment (BHT) is more valuable in lower GCS group (Fig. 2, left).
(2) BHT is more effective in younger age group (Fig. 2, right).
(3) BHT is more effective in lower normal blood pressure group (Fig. 3, left).
(4) BHT is more valuable in abnormal light reflex group (Fig. 3, right).
(5) BHT is more valuable in higher initial ICP groups (Fig. 4, left).
(6) BHT is more effective in higher body temperature on arrival group (Fig. 4, right).
(7) BHT is more valuable in abnormal basal cistern on CT group (Fig. 5, left).
(8) BHT is most effective in very high blood sugar on admission group (Fig. 5, right).

2.2 Discussion

The clinical effect of the brain hypothermia treatment was denied with RCT study of the severe brain injury in U.S.A. at 2001 report [4]. It is not necessary to deny all of them under the lack condition of other clinically effective brain protection treatment including drugs [5–7]. The study of the appropriate indication and methodology of the brain hypothermia like the following are necessary.

TABLE 2. Japan Neurotrauma Data Bank (JNTDB)

Ten Neurotraumatic emergency center in Japan
July 1998–June 2003
Glasgow Coma Scale (GCS): 8 or less
Over 6 years old patient
Survey items: 392
Registered total number: 1,002 cases
Outcome: Glasgow Outcome Scale (GOS) on discharge and final GOS (6–12 months).
Acute subdural hematoma, acute brain swelling (TCDB-CT classification III & IV), cerebral contusion and traumatic ICH (except acute epidural hematoma, DAI, CPA): 708 cases

TABLE 3. Characteristics of patients (708 cases)

	Non-hypothermia G	Hypothermia G
Case no.	579	129
Mean age	52.2 (6–98)	36.7 (6–76)
GCS on admission	4.74	5.14
Body temperature (lowest)		34.1 (30.8–37)
Brain temperature (lowest)		33.9 (29.3–37)
Hypothermic duration		1 day: 11
		3–5 days: 70
		Over 6 days: 45

TABLE 4. Results of each group (case number and percent)

	Non-hypothermia G		Hypothermia G	
	(1)	(2)	(1)	(2)
GR	32 (5.5)	51 (8.8)	10 (7.8)	22 (17.1)
MD	31 (5.4)	40 (6.9)	18 (14.0)	15 (11.6)
SD	82 (14.2)	49 (8.5)	34 (26.4)	25 (19.4)
VS	40 (6.9)	36 (6.2)	12 (9.3)	9 (7.0)
D	394 (68)	403 (69)	55 (42.6)	58 (45.0)

(1) GOS (on discharge); (2) GOS (final).
GOS, Glasgow Outcome Scale; GR, good recovery; MD, moderately disabled; SD, severely disabled; VS, vegetative survival; D, dead.

(1) How to decide the appropriate therapeutic window.
   ① age as the object (upper and lower limit of the aged and the infant respectively)
   ② pathophysiology as the good indication
   ③ severity of the brain injury
(2) appropriate target temperature?
(3) appropriate duration of the hypothermia?
(4) appropriate rewarming method? (duration, speed, linear or stepwise fashion)
(5) improvement of the general management (intra-vascular cooling can reduce the complication?)
(6) surface cooling or intravascular cooling?
(7) ICP oriented cooling is appropriate?

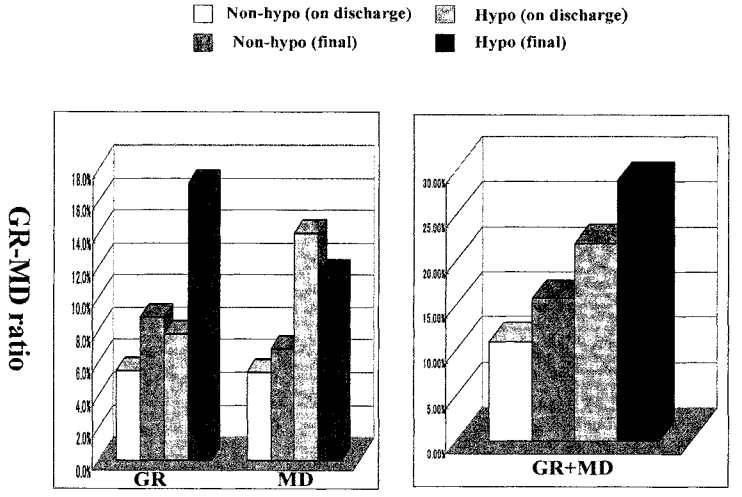


FIG. 1. Ratio of GR, MD (left) and GR + MD (right)

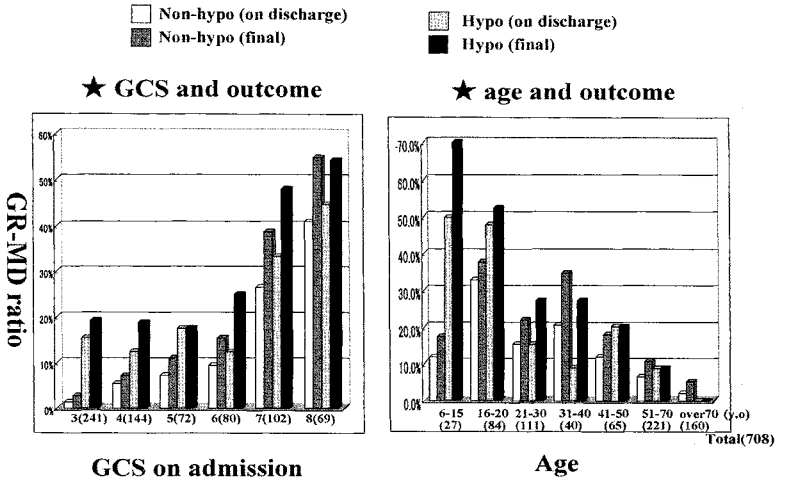


FIG. 2. Correlation between GCS on admission (left), age (right) and good outcome

2.3 Conclusions

(1) The most severe brain injury patients were difficult to rescue in the conventional treatment without brain hypothermia.
(2) The recovery and neuro-protective mechanism by brain hypothermia is different from the conventional one.

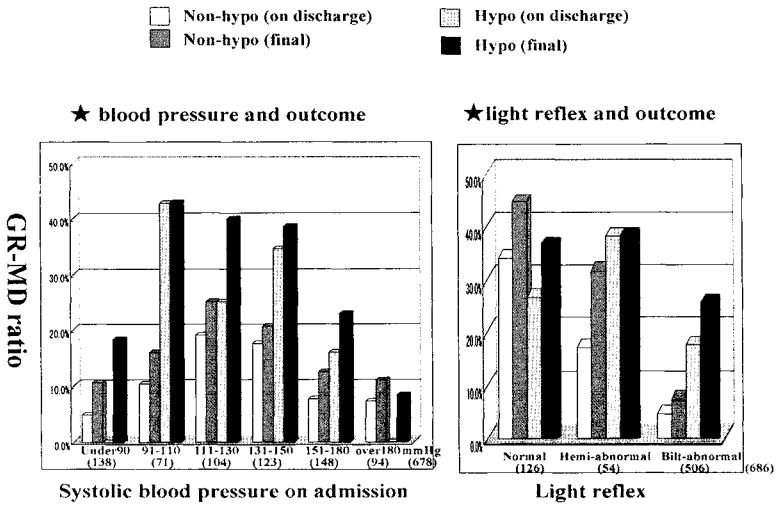


FIG. 3. Correlation between systolic blood pressure on admission (left), light reflex (right) and good outcome

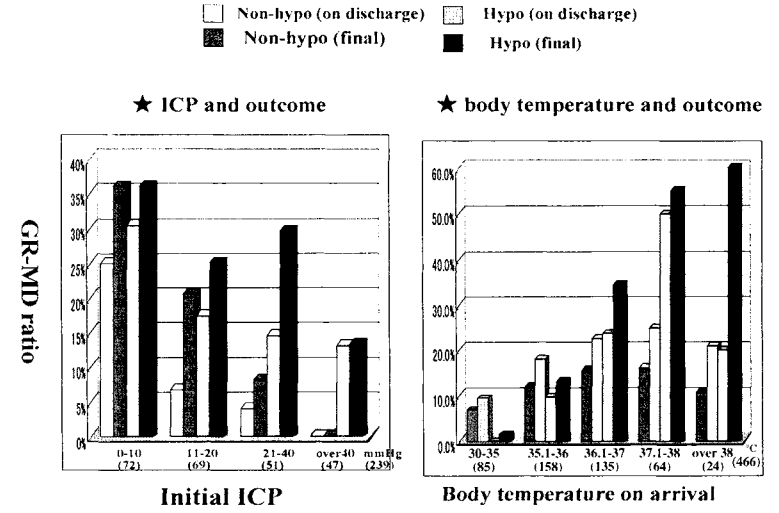


FIG. 4. Correlation between initial ICP (left), body temperature on arrival (right) and good outcome

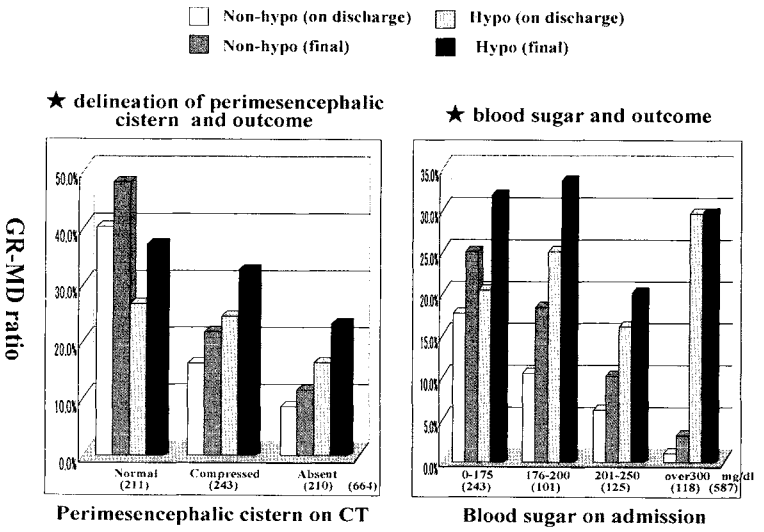


FIG. 5. Correlation between perimesencephalic cistern on CT (left), blood sugar on admission (right) and good outcome

References

1. Takasato Y, Masaoka H, Hayakawa T, et al (1999) Brain hypothermia therapy for severe brain injury. Interntional conference on recent advances in neurotraumatology (ICRAN), Monduzzi Editore, pp. 133–135
2. Takasato Y, Masaoka H, Ohta Y, et al (2004) Change of prognostic indicators of severe brain injury treated by brain hypothermia. 7th international neurotrauma symposium, Medimond, pp. 135–137
3. Dietrich WD, Alonso O, Busto R, et al (1994) Post-traumatic brain hypothermia reduces histipathological damage following concussive brain injury in the rat. Acta Neuropathol 87:250–258
4. Clifton GL, Miller ER, Choi SC, et al (2001) Lack of effect of induction of hypothermia after acute brain injury. N Engl J Med 344:556–563
5. Marion DW, Penrod LE, Kelsey SF, et al (1997) Treatment of traumatic brain injury with moderate hypothermia, N Engl J Med 336:540–546
6. Soukup J, Zauner A, Doppenberg EM, et al (2002) Realtionship between brain temperature, brain chemistry and oxygen delivery after severe human head injury: The effect of mild hypothermia. Neurol Res 24:161–168
7. Bramlett HM, Green EJ, Dietrich WD, et al (1995) Posttraumatic brain hypothermia provides protection from sensoriomotor and cognitive behavioral deficits. J neurotrauma 12:289–298

Therapeutic Moderate Hypothermia for Severe Traumatic Brain Injury: A Review

Donald W. Marion

Summary. Patients with severe TBI have been treated with hypothermia for more than 50 years, though it was not until the last 15 years that the efficacy of the treatment was systematically tested. This renewed interest in therapeutic hypothermia is attributed to the discovery that moderate levels of cooling (32–33°C) could be effective and were not associated with clinically significant adverse cardiac or coagulation effects observed with lower temperatures. During this time there have been at least 14 prospective randomized clinical trials (PRCT) of the use of hypothermia to improve outcomes following severe TBI. Combined, these trials enrolled more than 1,200 patients and found that the likelihood of a good outcome was 15% higher in those who were treated with hypothermia. At least 12 studies also have evaluated the effect of hypothermia on elevated intracranial pressure (ICP) and, with a single exception, have all found a significant reduction in ICP during the period of cooling. Concomitant laboratory investigations have defined several mechanisms whereby hypothermia may reduce secondary brain injury.

Key words. hypothermia, traumatic brain injury, intracranial pressure, secondary brain injury, clinical trials

1 Background

The use of hypothermia to treat patients with severe TBI was first reported by Fay in 1943, and Sedzimir in the 1950's [1,2]. These clinicians thought that cooling patients to as low as 27°C for 1–5 days after injury led to better than expected outcomes in some patients. Lundberg reported that hypothermia was as effective as osmotic diuretics for reducing elevated ICP, and had a more prolonged effect than hyperventilation [3]. James et al found that hypothermia caused a reduction of ICP in at least half of 40 patients with severe TBI they studied, and that the average decrease associated with hypothermia treatment was 41% [4]. However, concerns about

Senior Research Fellow, The Brain Trauma Foundation, New York, NY, U.S.A.

complications of hypothermia treatment, such as pneumonia, coagulopathy, and cardiac arrythmias, dampened enthusiasm for its use until approximately 15 years ago. In 1991 Clifton reported that cooling to only 32°C for as little as 4 h after injury was sufficient to significantly improve outcomes in a rodent model of TBI [5]. This was a critical finding since most of the complications of therapeutic hypothermia were attributed to cooling below 30°C and treatment for more than 48 h. Indeed, 3 independent Phase I clinical trials reported in 1993 found that there were no *clinically* significant complications attributable to therapeutic moderate hypothermia (32–34°C) when use for up to 48 h [6–8].

2 Mechanisms of Hypothermic Effect

The use of therapeutic hypothermia for severe TBI was initially based on the presumption that TBI caused a hypermetabolic state that was at least partially responsible for post traumatic brain swelling. Canine experiments conducted during the 1950's showed that, in the uninjured brain, both the cerebral metabolic rate of oxygen and the cerebral blood flow decreased by 6.7% for every degree C reduction in temperature from 35–25°C [9,10]. Others found that hypothermia led to significant preservation of high energy phosphate compounds in the injured brain [11]. More recent experimental studies of TBI and ischemia have shown hypothermia to be very effective in reducing elevated brain tissue or CSF levels of excitatory amino acids [12,13], lactate [14], and cytokines [15], diminishing the cellular inflammatory response [16,17], preserving the integrity of the blood-brain barrier [18,19], and decreasing cerebral edema [20] in addition to reducing the volume of damaged brain tissue [21] and improving both cognitive and functional outcomes [5,22,23]. Clinical studies show that TBI patients treated with hypothermia have a decrease in post traumatic prostanoid production [24] and lower CSF or brain tissue levels of inflammatory cytokines (IL-1ß, IL-6) [25,26], glutamate [26], and nerve growth factor [15], though not nitric oxide [27], when compared with normothermia patients. Hypothermia may increase the brain tissue partial pressure of oxygen and causes a decrease in the CMRO2, but does not effect post traumatic glucose metabolism [8,28,29].

3 Medical Complications Associated with Therapeutic Hypothermia

Hypothermia causes a decrease in the heart rate, cardiac index, and global cerebral blood flow [8,26,30]. However, with temperatures of 32°C or higher, none of these physiologic changes have been found to be clinically significant. Moderate hypothermia has not been found to increase the risk of cardiac arrythmias (except bradycardia) in approximately 1,200 patients enrolled in 9 separate clinical trials. Hypothermia does typically cause hypokalemia. Whole body potassium levels remain unchanged, but reducing the body temperature causes an intracellular migration of serum potassium and thereby reduces the blood level of this electrolyte. One study also found a significant decrease in serum phosphate, magnesium and calcium levels during the first 6 h after cooling, and suggested that there was a hypothermia induced increase in excretion of these molecules in the urine [31].

Moderate hypothermia (≥32°C) was associated with significant changes in the PT, PTT, or the platelet count in two clinical trials [6,32], but not in two other trials including the large NABIS: H trial [26,33]. In addition, an increase in the incidence of delayed post-traumatic intracranial hemorrhage in patients randomized to hypothermia has not been found [34], and no study has described an increase in hemorrhagic complications in the hypothermia group.

Hypothermia is associated with an increased risk of infection which may be related to the duration of cooling. One study found an increased incidence of pneumonia with cooling for as little as 48 h [32]. As many as 40–50% of patients cooled for longer than 3 days may develop pneumonia [35]. In one study of 41 patients assigned to hypothermia or normothermia, the patients in the hypothermia group had the same incidence of pneumonia and meningitis as the normothermia patients, but lymphocyte and neutrophil counts were significantly lower in the hypothermia patients and they had a significantly higher incidence of bacteremia [36]. When pneumonia occurred in the hypothermia patients it was much more fulminant and life-threatening. But none of the studies reviewed found a significant association between infection and worse outcomes in hypothermia patients.

4 Clinical Studies of the Efficacy of Therapeutic Hypothermia

An exhaustive search of the English language literature through February of 2005 has revealed 14 prospective randomized clinical trials of the use of therapeutic hypothermia for treatment of severe traumatic brain injury. Because of the large number of trials available for review, we have excluded from further discussion studies that enrolled fewer than 15 patients into both the hypothermia and control arms of the trial [24,37–39], failed to provide information about outcomes at 3 months or more after injury [37,40], or were not published in peer-reviewed journals [38]. Exclusion of these studies is unlikely to bias the conclusions of this report since the numbers are small, and some of the excluded studies that provided outcome data showed a benefit of cooling while others did not. In the case of two of these excluded studies, there is also a high likelihood that patients in those reports were included as part of larger studies subsequently published by the same authors, and included in the studies reviewed below [37,39].

Among the 9 remaining clinical trials a total of 1,243 patients with severe TBI were enrolled (Table 1). All were prospective randomized clinical trials (PRCTs), but there was considerable variability regarding the duration of hypothermia (24 h to 14 days), time of initiation of treatment (within 6 h of injury *vs* only after conventional ICP treatment failed), and length of follow up (3 months to 2 years). The target depth of cooling ranged from 32 to 35°C. Relevant medical complications, such as the incidence of infections, cardiac arrythmias, or coagulation abnormalities, were not always reported. All but two of the trials were conducted at a single hospital. The two multicenter trials each enrolled patients from 11 different hospitals.

The outcomes for the individual trials are provided in Table 1. For the entire group of 1,218 patients available for follow up, good outcomes (GOS 4, 5) were observed in 330/613 (54%) of patients treated with hypothermia, and 236/605 (39%) of patients kept normothermic. Thus, the likelihood of a good outcome was 15% higher for the

TABLE 1. Effect of hypothermia on outcome

Source	Study design	Setting	Sample	Intervent.	Length of f/u	Measures	Analysis	Good outcome (GOS 4, 5) Hypothermia (%)	Normothermia (%)	*P* value	Caveats	Level of evid
J Neurosurg 1993 79: 363[8]	PRCT	Single hospital	*n* = 33/Severe TBI/Adults	34°C/48 h	6 months	GOS	Effect of hypothermia on outcome	38	6	$P > 0.05$		I
J Neurotrau 1993 10:263[6]	PRCT	Single hospital	*n* = 46/Severe TBI/Adults	32–33°C/ 48 h	3 months	GOS	Effect of hypothermia on outcomes	52	36	$P > 0.287$	PT sig. prolonged	I
N Engl J Med 1997 336:540[26]	PRCT	Single hospital	*n* = 82/Severe TBI/Adults	32–33°C/ 24 h	6 months	GOS	Effect of hypothermia on outcomes	56	33	$P = 0.05$		I
J Neurosurg 2000 93:546[35]	PRCT	Single hospital	*n* = 87/Severe TBI/Adults	33–35°C/ 3–14 days	1 year	GOS	Effect of hypothermia on outcome	46.5	27	$P < 0.05$		I
J Neurosurg 2001 94:50[32]	PRCT	11 hospital	*n* = 91/Severe TBI/Adults	34°C/48 h	3 months	GOS	Effect of hypothermia on outcomes	46	59	$P > 0.99$	Thrombocytopenia sig. more common, and more pneumonia in hypopts	I
N Engl J Med 2001 344:556[33]	PRCT	11 hospitals	*n* = 392/Severe TBI/Adults	33°C/48 h	6 months	GOS	Effect of hypothermia on outcomes	43	43	$P = 0.99$	Significant intercenter differences in acute care [45]	I
Clin Neurol Neurosurg 2002 104:318[41]	PRCT	Single hospital	*n* = 30/Severe TBI/Adults	34°C/72 h	6 months	GOS	Effect of hypothermia on outcomes	87	47	$P = 0.0843$		I
Surg Neurol 2003 59:381[42]	PRCT	Single hospital	*n* = 396/Severe TBI/Adults	32–35°C/ 1–7 days	6 months	GOS	Effect of hypothermia on outcomes	62	38	$P < 0.05$		I
Chin J Traumatol 2005 8:27[43]	PRCT	Single hospital	*n* = 86/Severe TBI/Adults	33–35°C/ 3–5 days	2 years	GOS	Effect of hypothermia on outcomes	65.1	37.2	$P < 0.05$		I

patients treated with hypothermia. ($P < 0.01$, chi sq using dichotomized GOS) Two of the studies each enrolled nearly 400 patients and accounted for 2/3 of the total, thereby having a major impact on the results. But these two large trials arrived at opposite conclusions. In a multicenter study that enrolled 392 patients, no benefit of hypothermia treatment was found: 43% of the patients in both the hypothermia and normothermia groups had a good outcome at 6 months. However, significant intercenter differences in CPP and intravascular volume management, and in the number of patients enrolled from each center, were identified as problems that may have confounded the analysis of the outcome data [44,45]. In a single center study that enrolled 396 patients, good outcomes were seen in 62% of the hypothermia patients but in only 38% of the normothermia patients at 1 year follow up, and these differences were statistically significant.

Given the complexities of contemporary acute care of patients with severe TBI and the treatment biases of the multiple critical care physicians typically involved, some have suggested that it may not be possible to conduct a multicenter clinical trial for TBI that reliably evaluates the efficacy of the study treatment [46]. Among the PRCTs reviewed for this guideline, all but the 2 multicenter trials found at least a trend toward improved outcomes in the hypothermia groups. Analysis of data from just the 7 single center studies reveals that 222/378 (59%) of patients treated with hypothermia, and 133/381 (35%) of the patients kept normothermic, had good outcomes—a 24% difference ($P < 0.001$, chi sq).

In support of the potential benefit of therapeutic hypothermia is the observation that in all but one of the PRCTs where the data was available, as well as several case series, cooling was found to result in a significant decrease in ICP (Table 2). Elevated ICP is a well known independent risk factor for poor outcomes, though it has not been proven that reducing high ICPs results in improved outcomes.

5 Summary

A large number of prospective randomized clinical trials have evaluated the use of therapeutic hypothermia for patients with severe traumatic brain injury, and a meta-analysis of these studies reveals that hypothermia treatment results in a 15% greater likelihood of good outcomes. The two multicenter trials did not find benefit with this treatment, while all of the single center studies found at least a trend toward improved outcomes and the largest single center trial found significant benefit. Significant intercenter differences in critical acute care parameters have been reported for the largest of the multi-center trials, and raise concern about the results of that study.

However, the use of hypothermia cannot be recommended for all trauma centers because the multicenter trials did not find benefit with the use of this therapy. Because only the single center trials in hospitals that enrolled a relatively large number of patients found benefit, the evidence supports limiting the use of hypothermia to experienced neurotrauma programs that can carefully monitor the physiologic changes associated with hypothermia and immediately respond to those changes. In addition, because of the conflicting findings of the two largest prospective randomized trials [33,42], therapeutic hypothermia cannot be recommended at the level of a standard.

TABLE 2. Effect of hypothermia on ICP (during the period of cooling)

Source	Study design	Setting/ Population	Sample	Intervent.	Length of F/U	Measures	Analysis	Results	Level of evidence
J Neurosurg 1993 79:363[8]	PRCT	Single hospital	$n = 33$/Severe TBI/Adults	34°C/48 h	ICU	ICP	Effect of hypothermia on ICP	Significant reduction of ICP	I
J Neurotrauma 1993 10:263[6]	PRCT	Single hospital	$n = 46$/Severe TBI/Adults	32–33°C/ 48 h	ICU	ICP	Effect of hypothermia on ICP	No significant change in ICP	I
J Neurosurg 1996 85:533[30]	Case series	Single hospital	$n = 10$/Severe TBI/Adults	32.5–33°C/ 25 h	ICU	ICP	Effect of hypothermia on ICP	Significant reduction of ICP	II
N Engl J Med 1997 336:540[26]	PRCT	Single hospital	$n = 82$/Severe TBI/Adults	32–33°C/ 24 h	ICU	ICP	Effect of hypothermia on ICP	Significant reduction of ICP	I
Acta Neurochir Suppl 1998 71:22[47]	Case series	Single hospital	$n = 23$/Severe TBI/Adults	32–36°C/1–5 days	ICU	ICP	Effect of hypothermia on ICP	Significant reduction of ICP	II
Neurosurg 1998 42:1065[48]	Case series	Single hospital	$n = 9$/Severe TBI/Adults	35°C/1–6 days	ICU	ICP	Effect of hypothermia on ICP	Significant reduction of ICP	II
No Shinkei Geka 2000 28:983[49]	Case series	Single hospital	$n = 9$/Severe TBI/Children	33–34°C/ 3–21 days	ICU	ICP	Effect of hypothermia on ICP	Significant reduction of ICP	II
J Neurosurg 2000 93:546[35]	PRCT	Single hospital	$n = 87$/Severe TBI/Adults	33–35°C/ 3–14 days	ICU	ICP	Effect of hypothermia on ICP	Significant reduction of ICP	I
N Engl J Med 2001 344:556[33]	PRCT	11 hospitals	$n = 392$/Severe TB1/Adults	33°C/48 h	ICU	ICP	Effect of hypothermia on ICP	Significant reduction in % of patients with ICP > 120 mm Hg	I
Crit Care Med 2002 30:2742[50]	PRCT	Single hospital	$n = 21$/Severe TBI/Children	32–35°C/48 h	ICU	ICP	Effect of hypothermia on ICP	Significant reduction of ICP	I
Clin Neurol Neurosurg 2002 104:318[41]	PRCT	Single hospital	$n = 30$/Severe TBI/Adults	34°C/72 h	ICU	ICP	Effect of hypothermia on ICP	Significant reduction of ICP	I
Neurosurg 2003 52:102[51]	Case series	Single hospital	$n = 31$/Severe TBI/Adults	33°C/48–72 h	ICU	ICP	Effect of hypothermia on ICP	Significant reduction of ICP	II

6 Recommendations

Therapeutic moderate hypothermia (32–35°C) for 48 h or less may be considered for patients with severe TBI. However, use of this treatment is only recommended at experienced neurotrauma programs that thoroughly understand the physiologic changes associated with hypothermia, and are capable of immediately responding to those changes. Hypotension and hypovolemia must be avoided. Moderate hypothermia for 48 h or less may also be considered for the treatment for elevated ICP.

References

1. Fay T (1959) Early experiences with local and generalized refrigeration of the human brain. J Neurosurg 16:239–259
2. Sedzimir CB (1959) Therapeutic hypothermia in cases of head injury. J Neurosurg 16:407–414
3. Lundberg N, Troupp H, Lorin H (1965) Continuous recording of the ventricular-fluid pressure in patients with severe acute traumatic brain injury. A preliminary report. J Neurosurg 22:581–590
4. James HE, Langfitt TW, Kumar VS, et al (1977) Treatment of intracranial hypertension. Analysis of 105 consecutive, continuous recordings of intracranial pressure. Acta Neurochir (Wien) 36:189–200
5. Clifton GL, Jiang JY, Lyeth BG, et al (1991) Marked protection by moderate hypothermia after experimental traumatic brain injury. J Cereb Blood Flow Metab 11:114–121
6. Clifton GL, Allen S, Barrodale P, et al (1993) A phase II study of moderate hypothermia in severe brain injury. J Neurotrauma 10:263–271
7. Marion DW, Obrist WD, Carlier PM, et al (1993) The use of moderate therapeutic hypothermia for patients with severe head injuries: A preliminary report. J Neurosurg 79:354–362
8. Shiozaki T, Sugimoto H, Taneda M, et al (1993) Effect of mild hypothermia on uncontrollable intracranial hypertension after severe head injury. J Neurosurg 79:363–368
9. Rosomoff HL (1966) Relationship of metabolism to hypothermia. Res Publ Assoc Res Nerv Ment Dis 41:116–126
10. Rosomoff HL, Holaday DA (1954) Cerebral blood flow and cerebral oxygen consumption during hypothermia. Am J Physiol 179:85–88
11. Donnelly C, Frobese AS, Stone HH (1956) The effect of lowered body temperature on the cerebral hemodynamics and metabolism of man. Surg Gynecol Obstet 103:313–317
12. Busto R, Globus MY, Dietrich WD, et al (1989) Effect of mild hypothermia on ischemia-induced release of neurotransmitters and free fatty acids in rat brain. Stroke 20: 904–910
13. Lyeth BG, Jiang JY, Robinson SE, et al (1993) Hypothermia blunts acetylcholine increase in CSF of traumatically brain injured rats. Mol Chem Neuropathol 18:247–256
14. Jiang JY, Liang YM, Luo QZ, et al (2004) Effect of mild hypothermia on brain dialysate lactate after fluid percussion brain injury in rodents. Neurosurgery 54:713–717
15. Goss JR, Styren SD, Miller PD, et al (1995) Hypothermia attenuates the normal increase in interleukin 1 beta RNA and nerve growth factor following traumatic brain injury in the rat. J Neurotrauma 12:159–167
16. Chatzipanteli K, Alonso OF, Kraydieh S, et al (2000) Importance of posttraumatic hypothermia and hyperthermia on the inflammatory response after fluid percussion brain injury: Biochemical and immunocytochemical studies. J Cereb Blood Flow Metab 20:531–542

17. Whalen MJ, Carlos TM, Clark RS, et al (1997) The relationship between brain temperature and neutrophil accumulation after traumatic brain injury in rats. Acta Neurochir Suppl (Wien) 70:260–261
18. Jiang JY, Lyeth BG, Kapasi MZ, et al (1992) Moderate hypothermia reduces blood-brain barrier disruption following traumatic brain injury in the rat. Acta Neuropathol (Berl) 84:495–500
19. Smith SL, Hall ED (1996) Mild pre- and posttraumatic hypothermia attenuates blood-brain barrier damage following controlled cortical impact injury in the rat. J Neurotrauma 13:1–9
20. Kawai N, Nakamura T, Okauchi M, et al (2000) Effects of hypothermia on intracranial pressure and brain edema formation: Studies in a rat acute subdural hematoma model. J Neurotrauma 17:193–202
21. Dietrich WD, Alonso O, Busto R, et al (1994) Post-traumatic brain hypothermia reduces histopathological damage following concussive brain injury in the rat. Acta Neuropathol (Berl) 87:250–258
22. Dixon CE, Markgraf CG, Angileri F, et al (1998) Protective effects of moderate hypothermia on behavioral deficits but not necrotic cavitation following cortical impact injury in the rat. J Neurotrauma 15:95–103
23. Lyeth BG, Jiang JY, Liu S (1993) Behavioral protection by moderate hypothermia initiated after experimental traumatic brain injury. J Neurotrauma 10:57–64
24. Aibiki M, Maekawa S, Yokono S (2000) Moderate hypothermia improves imbalances of thromboxane A2 and prostaglandin I2 production after traumatic brain injury in humans. Crit Care Med 28:3902–3906
25. Aibiki M, Maekawa S, Ogura S, et al (1999) Effect of moderate hypothermia on systemic and internal jugular plasma IL-6 levels after traumatic brain injury in humans. J Neurotrauma 16:225–232
26. Marion DW, Penrod LE, Kelsey SF, et al (1997) Treatment of traumatic brain injury with moderate hypothermia. N Engl J Med 336:540–546
27. Clark RS, Kochanek PM, Obrist WD, et al (1996) Cerebrospinal fluid and plasma nitrite and nitrate concentrations after head injury in humans. Crit Care Med 24:1243–1251
28. Zhang S, Zhi D, Lin X, et al (2002) Effect of mild hypothermia on partial pressure of oxygen in brain tissue and brain temperature in patients with severe head injury. Chin J Traumatol 5:43–45
29. Zhao W, Alonso OF, Loor JY, et al (1999) Influence of early posttraumatic hypothermia therapy on local cerebral blood flow and glucose metabolism after fluid-percussion brain injury. J Neurosurg 90:510–519
30. Metz C, Holzschuh M, Bein T, et al (1996) Moderate hypothermia in patients with severe head injury: Cerebral and extracerebral effects. J Neurosurg 85:533–541
31. Polderman KH, Peerdeman SM, Girbes AR (2001) Hypophosphatemia and hypomagnesemia induced by cooling in patients with severe head injury. J Neurosurg 94: 697–705
32. Shiozaki T, Hayakata T, Taneda M, et al (2001) A multicenter prospective randomized controlled trial of the efficacy of mild hypothermia for severely head injured patients with low intracranial pressure. Mild Hypothermia Study Group in Japan. J Neurosurg 94:50–54
33. Clifton GL, Miller ER, Choi SC, et al (2001) Lack of effect of induction of hypothermia after acute brain injury. N Engl J Med 344:556–563
34. Resnick DK, Marion DW, Darby JM (1994) The effect of hypothermia on the incidence of delayed traumatic intracerebral hemorrhage. Neurosurgery 34:252–255
35. Jiang J, Yu M, Zhu C (2000) Effect of long-term mild hypothermia therapy in patients with severe traumatic brain injury: 1-year follow-up review of 87 cases. J Neurosurg 93:546–549

36. Ishikawa K, Tanaka H, Shiozaki T, et al (2000) Characteristics of infection and leukocyte count in severely head-injured patients treated with mild hypothermia. J Trauma 49:912–922
37. Clifton GL, Allen S, Berry J, et al (1992) Systemic hypothermia in treatment of brain injury. J Neurotrauma 9 (Suppl 2):S487–S495
38. Hirayama T, Katayama Y, Kano T, et al (1994) Impact of moderate hypothermia on therapies for intracranial pressure control in severe traumatic brain injury. In: Nagai H, Ishii S, Maeda M (eds) Intracranial pressure IX: 9th International Symposium held in Nagaya, Japan, 1994. Springer-Verlag, New York, pp 233–236
39. Shiozaki T, Kato A, Taneda M, et al (1999) Little benefit from mild hypothermia therapy for severely head injured patients with low intracranial pressure. J Neurosurg 91: 185–191
40. Yan Y, Tang W (2001) Changes of evoked potentials and evaluation of mild hypothermia for treatment of severe brain injury. Chin J Traumatol 4:8–13
41. Gal R, Cundrle I, Zimova I, et al (2002) Mild hypothermia therapy for patients with severe brain injury. Clin Neurol Neurosurg 104:318–321
42. Zhi D, Zhang S, Lin X (2003) Study on therapeutic mechanism and clinical effect of mild hypothermia in patients with severe head injury. Surg Neurol 59:381–385
43. Qiu WS, Liu WG, Shen H, et al (2005) Therapeutic effect of mild hypothermia on severe traumatic head injury. Chin J Traumatol 8:27–32
44. Choi SC, Bullock R (2001) Design and statistical issues in multicenter trials of severe head injury. Neurol Res 23:190–192
45. Clifton GL, Choi SC, Miller ER, et al (2001) Intercenter variance in clinical trials of head trauma—experience of the National Acute Brain Injury Study: Hypothermia. J Neurosurg 95:751–755
46. Safar P, Kochanek PM (2001) Lack of effect of induction of hypothermia after acute brain injury. N Engl J Med 345:66–61
47. Nara I, Shiogai T, Hara M, et al (1998) Comparative effects of hypothermia, barbiturate, and osmotherapy for cerebral oxygen metabolism, intracranial pressure, and cerebral perfusion pressure in patients with severe head injury. Acta Neurochir Suppl 71:22–26
48. Tateishi A, Soejima Y, Taira Y, et al (1998) Feasibility of the titration method of mild hypothermia in severely head-injured patients with intracranial hypertension. Neurosurgery 42:1065–1069
49. Takahashi I, Kitahara T, Endo M, et al (2000) [Clinical analysis of hypothermia in children with severe head injury]. No Shinkei Geka 28:983–989
50. Biswas AK, Bruce DA, Sklar FH, et al (2002) Treatment of acute traumatic brain injury in children with moderate hypothermia improves intracranial hypertension. Crit Care Med 30:2742–2751
51. Tokutomi T, Morimoto K, Miyagi T, et al (2003) Optimal temperature for the management of severe traumatic brain injury: Effect of hypothermia on intracranial pressure, systemic and intracranial hemodynamics, and metabolism. Neurosurgery 52:102–111

Early Decompressive Surgery for Spinal Cord Injury: Rationale Based on Experimental Study

TETSUYA MORIMOTO, YASUSHI SHIN, RINSEI TEI, and YASUO HIROKAWA

Summary. We have made an experimental study on secondary spinal cord ischemia following initial spinal cord injury. The spinal cord injury was made at Th10 level by the clip compression method in rats. Spinal cord blood flow and arterial diameter were measured simultaneously at both rostral and caudal to the cord injury level. There is a significant decrease of blood flow and arterial diameter at both rostral and caudal to the injury site. The ischemic zone evaluated histologically tended to expand more diffusely in the rostal direction than in the caudal direction. In the pre-injury stage, both CO2 reactivity and autoregulation were present in the spinal cord. Following the clip injury, CO2 reactivity and autoregulation were both impaired in the areas 7 mm adjacent to the impact site. Correlation coefficients suggested that the rostral spinal cord tended to sustain more injury than the caudal spinal cord. Based on this experimental study, we have advocated an early decompression surgery for the patients with cervical spinal cord injury. We also made clinical study on the effectiveness of decompression surgery. There were 32 cases of surgical treatment and 27 cases of conservative treatment. A two step improvement in Frankel grading was observed in 6 cases in the surgically treated group while no two step improvement was observed in the conservative group. There is still a debate on the management of spinal cord injury regarding the surgical treatment such as approach, timing of the surgery, and the indication of instrumentation. We believe that early decompression surgery is the most important step to obtain better clinical outcome in patients with spinal cord injury.

Key words. spinal cord injury, decompression surgery, spinal cord blood flow

Section chief of Neurosurgery, Osaka Police Hospital, 10-31, Kitayama-cho, Tennoji-ku, Osaka, Japan

Acetazolamide Vasoreactivity Evaluated by Transcranial Ultrasonic Power Harmonic Imaging and Doppler Sonography

Toshiyuki Shiogai[1], Aki Morisaka[1], Yuuka Arima[1], Kaori Ikeda[1], Natsuko Takayasu[2], Yoshinari Nagakane[2], Kenji Yoshikawa[2], Toshiki Mizuno[2], Masanori Nakagawa[2], and Hiroshi Furuhata[3]

Summary. Transcranial ultrasonic power harmonic imaging (PHI) can more easily identify brain tissue perfusion than gray-scale imaging. To overcome the problems, particularly due to depth-dependent ultrasound attenuation, and to establish the clinical significance, we evaluated acetazolamide (ACZ) vasoreactivity tests utilizing transcranial PHI in comparison with Doppler sonography (TCD). Methods: The subjects were 25, predominantly stroke patients, with almost half having left side lesions. TCD-measured time-averaged maximum velocity (Vmax) in the middle and posterior cerebral arteries, and PHI maximum size, peak intensity (PI), and time-to-peak intensity (TPI) of the contrast area based on a time-intensity bolus curve from the axial diencephalic image, were evaluated bilaterally. Vasoreactivity was assessed by comparisons before and after ACZ administration, in terms of: (a) TCD Vmax, (b) PHI contrast area size, PI, and TPI, and (c) the relationship of vasoreactivity (%Δ) between PHI and TCD. Results: Increases in all compared factors, except for TPI, were more significant, and correlations between PHI and TCD vasoreactivity were more significant and sensitive, in the right side than in the left. Conclusions: Transcranial PHI allows quicker and easier evaluation of vasoreactivity in the brain tissue, and will have clinical value in pathophysiological follow-up and therapeutic effectiveness determination in neurointensive care settings.

Key words. transcranial power harmonic imaging, brain tissue perfusion, echo-contrast agents, transcranial Doppler sonography, acetazolamide vasoreactivity

[1] Department of Clinical Neurosciences, Kyoto Takeda Hospital, Minamikinuta-cho 11, Nishinanajo, Shimogyo-ku, Kyoto 600-8884, Japan, [2] Department of Neurology, Kyoto Prefectural University of Medicine, Kamigyo-ku, Kyoto, and [3] Medical Engineering Laboratory, Tokyo Jikei University School of Medicine, Minato-ku, Tokyo, Japan

1 Introduction

Transcranial ultrasonic harmonic imaging utilizing echo-contrast agents (ECA) has been introduced for repeatable non-invasive bedside measurements of brain tissue perfusion. Quantitative parameters from time-intensity curve analysis after a bolus ECA injection have been evaluated [1–4] and correlated with dynamic CT [3,5] and perfusion magnetic resonance imaging (MRI) [6]. However, quantitative reliability has not yet been established, mainly due to skull- and depth-dependent attenuation of the ultrasound signals [1–3]. Furthermore, the dye-dilution principle [7] commonly utilized in neuroradiological perfusion imaging would not be applicable to bolus ultrasonic kinetics due to the additional problems of ECA bubble saturation [8] and shadowing effects [9].

To overcome problems of intravenous bolus kinetics, refill kinetics [10], diminution kinetics [11] utilizing constant ECA intravenous infusion, and depletion kinetics after bolus ECA injection [12] have been tried. However, an optimal method has yet to be established.

In a different approach to overcome the problems, we have introduced acetazolamide (ACZ) vasoreactivity tests for quantitative evaluation at the same depth on gray-scale harmonic images, and correlated these with transcranial Doppler sonography (TCD) and dynamic CT [5]. In comparison with gray-scale harmonic imaging and power harmonic imaging (PHI), harmonic power Doppler imaging on harmonic B-mode images, exhibit the welcome and distinct feature of well-defined and easily identified contrast areas [13].

The objective of this study is to evaluate the reliability of ACZ vasoreactivity tests utilizing transcranial PHI in comparison with TCD and to consider the clinical significance for neurointensive care settings.

2 Methods

The subjects were 25 neurological patients (ages 35–90, mean 65; 21 male and 4 female). Primary diagnoses were 19 stroke (12 ischemic, 7 hemorrhagic), 2 degenerative diseases, 2 head injuries, and 2 others. Site of brain parenchymal lesions on the basis of CT and/or MRI were left hemisphere in 12 (48%), right hemisphere in 6 (24%), both hemispheres in 4 (16%), and diffuse in 3 (12%).

Utilizing a SONOS 5500 S4 transducer (Philips Medical Systems), open temporal acoustic windows had been previously confirmed. Transient response PH images taken every 2 seconds after a 7 ml-bolus Levovist injection (300 mg/ml) via antecubital vein were evaluated bilaterally. The investigation depth was 12 cm with a focus on 6 cm. The PHI settings were mechanical index 1.6, system gain 75, compression 70, color gain 40%, threshold 10, pulse repetition frequency 3.9 KHz, and filter 4. PH images were evaluated in an axial diencephalic plane via bilateral temporal windows. Data was stored on an MO disk for the following analyses. PHI contrast area size was measured by Scion Image (Beta 4.02 for Windows 95 to XP, Scion Corporation). Peak intensity (PI) and time-to-peak intensity (TPI) based on time-intensity curve analysis were measured by QLAB (Philips Medical Systems).

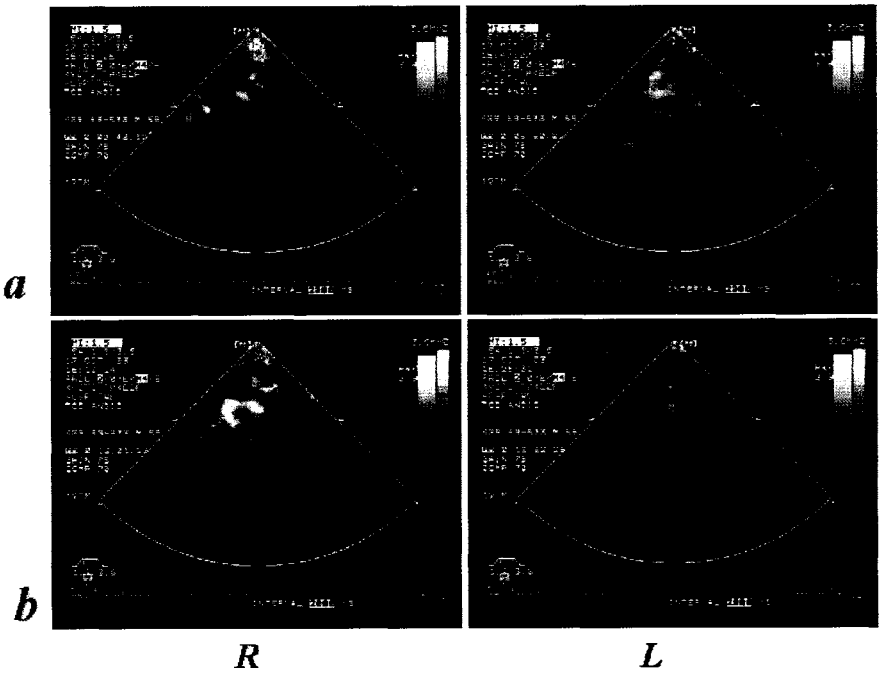


FIG. 1. Acetazolamide (ACZ) vasoreactivity tests by transcranial power harmonic imaging (PHI) in a 55-year-old subject were performed 5 months after atherothrombotic infarction caused by the left internal carotid artery occlusion. Bilateral images (R, right; L, left) are represented before (a) and after (b) 500 mg ACZ bolus intravenous injection. Despite increased contrast area size after ACZ (b) in the right side (R), decreased size in the left side (L) is probably due to a steal phenomenon

At rest, time-averaged maximum velocity (Vmax) in the middle and posterior cerebral arteries (MCA and PCA) was measured by TCD on both sides. The PHI was evaluated at rest on both sides, 15 and 30 min after a 500 mg Diamox intravenous injection via right and left temporal windows, respectively (Fig. 1). TCD Vmax in the ipsilateral MCA and PCA was measured just before PHI. The relative changes (%Δ) of TCD Vmax and PHI parameters were calculated at rest and after ACZ administration (parameters after ACZ—parameters at rest/parameters at rest ×100).

Assessments were based on comparisons conducted before and after ACZ in terms of: (a) TCD Vmax in the MCA and PCA, (b) PHI parameters; contrast area size, PI, and TPI, (c) Pearson's correlation coefficients (r) between Vmax (%Δ) and the PHI parameters (%Δ) and (d) Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and index of validity (true positives plus true negatives divided by the total number of cases) [14] for diagnostic accuracy of TCD Vmax (%Δ) in predicting HPI contrast area size (%Δ).Utilizing a paired-test and one-way analysis of variance, statistical significance was set at $P > 0.05$. Informed consent was obtained from patients and/or patients' family members before the study commenced.

TABLE 1. Values at rest and after acetazolamide (ACZ) administraion of transcranial Doppler sonography (TCD) and power harmonic imaging (PHI)

	At rest	ACZ
TCD Vmax (cm/s)		
MCA		
R	55.3 ± 20.7	75.5 ± 36.0***
L	54.1 ± 22.8	70.6 ± 37.7**
PCA		
R	34.4 ± 11.4	44.9 ± 13.7***
L	38.6 ± 16.7	47.2 ± 23.0*
PHI		
Contrast area size (cm^2)		
R	13.2 ± 11.4	17.7 ± 10.2***
L	13.2 ± 8.93	13.6 ± 8.30
Peak intensity (AU^2)		
R	17.1 ± 9.80	20.6 ± 11.6**
L	17.4 ± 11.8	16.6 ± 9.84
Time to peak intensity(s)		
R	24.4 ± 9.13	22.2 ± 9.31
L	23.0 ± 8.09	24.4 ± 7.26

All data given as mean values ± SD.
Vmax, time-averaged maximum velocity; MCA, middle cerebral artery; PCA, posterior cerebral artery; R, right; L, left.
* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ *vs* values at rest.

3 Results

3.1 *Values at Rest and after ACZ Administration* (Table 1)

There were no significant lateral differences in TCD and PHI values at rest. After ACZ, significant increases in TCD Vmax were more obvious in the right MCA and PCA ($P < 0.001$) than in the left MCA ($P < 0.01$) and PCA ($P < 0.05$). Contrast area size and PI increased significantly only in the right side ($P < 0.001$, $P < 0.01$, respectively). Despite the fact that a tendency of decreased TPI after ACZ was observed only in the right side, however, there were no significant TPI changes on either side.

3.2 *Correlation between PHI and TCD Vasoreactivity (%Δ)* (Table 2)

Close correlations of Vmax in the right MCA with contrast area size ($r = 0.79$, $P < 0.0001$) and with PI ($r = 0.75$, $P < 0.0001$) were more obvious than that of Vmax in the right PCA with contrast area size ($r = 0.51$, $P < 0.01$) and with PI ($r = 0.4$, $P < 0.05$). Regarding correlation with Vmax in the left MCA and PCA, the contrast area size and PI were not significant. In terms of TPI, there were no significant correlations with Vmax in the right MCA or bilateral PCA. A significant negative correlation between TPI and Vmax in the left MCA was observed.

TABLE 2. Correlation coefficient (r) of vasoreactivity (%Δ) between TCD and PHI parameters

	TCD			
	%Δ Vmax (R)		%Δ Vmax (L)	
	MCA	PCA	MCA	PCA
PHI				
Contrast area size (%Δ)	0.79***	0.51**	−0.23	0.18
Peak intensity (%Δ)	0.75***	0.4*	−0.28	0.21
Time-to-peak intensity (%Δ)	0.01	−0.37	−0.55*	0.13

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.0001$.

TABLE 3. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and index of validity for diagnostic accuracy of TCD Vmax (%Δ) in predicting PHI contrast area size (%Δ)

	TCD			
	%Δ Vmax (R)		%Δ Vmax (L)	
	MCA	PCA	MCA	PCA
HPI contrast area size (%Δ)				
Sensitivity	71	56	13	28
Specificity	70	53	60	71
PPV	77	42	25	20
NPV	64	67	46	77
Index of validity	78	79	56	61

Threshold at %Δ = 30.

3.3 Diagnostic Accuracy of TCD Vmax (%Δ) in Predicting PHI Contrast Area Size (%Δ) (Table 3)

When setting the threshold at %Δ = 30, sensitivity and PPV for diagnostic accuracy of TCD Vmax in predicting PHI contrast area size (%Δ) were higher in the right MCA than in the left MCA or bilateral PCA. Specificity was almost the same in both sides. However, the highest NPV was observed in the left PCA.

4 Discussion

Despite there being no lateral differences in TCD and PHI values at rest, significant increases of Vmax in the MCA and PCA after ACZ administration were more apparent in the right side than in the left side. Increases of PHI contrast area size and PI after ACZ were significant only in the right. Furthermore, correlations of TCD Vmax with PHI contrast area size and PI increases were closer and significant only in the right, rather than in the left. Additionally, in terms of diagnostic accuracy of TCD Vmax increase in predicting PHI contrast area size increases, sensitivity and PPV were both higher in the right than in the left.

We should take into account at least two related factors, which can cause these lateral differences of PHI contrast area size and PI increases after ACZ. Firstly, the presence of parenchymal pathological lesions in the side of PHI ACZ testing is likely to influence the results. In this study, almost half of all subject patients had left side lesions. PHI contrast area visualization is necessary to transmit acoustic power high enough for ECA bubble destruction in preserved capillaries in the viable brain tissue. For transcranial insonation, the contrast area size of PHI tends to be smaller than that of gray-scale harmonic imaging [13]. This is because PHI contrast effects necessitate a higher PI increase than in gray scale imaging. After ACZ, parenchymal blood flow increase in association with Vmax increases resulted in contrast area and PI increases in the non-lesion right side. In the lesion left side after ACZ, even if Vmax increases to some degree for preserved viable brain in the MCA and PCA territory, parenchymal blood flow does not always increase enough to increase contrast area size and PI. Furthermore, different ACZ effects on TCD Vmax, PHI contrast area, and PI resulted in the poor correlation of vasoreactivity between TCD and PHI and lower diagnostic accuracy of vasoreactivity, as evaluated by TCD for predicting PHI vasoreactivity.

Secondary, the time course of ACZ effects might result in lateral differences of vasoreactivity. Due to technical problems, PHI evaluation is limited mainly to a unilateral hemisphere via an ipsilateral temporal window. Therefore, in this study's protocol, from ACZ administration, PHI was evaluated after 15 min in the right hemisphere and 30 min in the left hemisphere. In a study of healthy normal subjects, ACZ effects for Vmax increase were stable during 10 to 30 min [15]. However, maximum peak of Vmax increase was obtained 15 min after ACZ and was followed by a slight decrease of ACZ effects [16]. In our neurological (mainly stroke) patients, ACZ effects for TCD Vmax and PHI parameters may differ, particularly 30 min after ACZ in the lesion left side. Further studies utilizing a bilateral approach [4] will hopefully resolve this problem.

In terms of PHI TPI of this study, there were no significant changes on both sides. Furthermore, no significant positive correlations between PHI TPI and TCD Vmax were identified. In ultrasonic quantification of brain tissue perfusion, depth- and skull- dependent attenuation of the ultrasound signals is the most important problem. A recent study utilizing gray-scale harmonic imaging suggested that TPI and positive gradient (PI divided by TPI) are the most robust and reliable parameters in-vitro bolus kinetics of SonoVue [17]. A comparative study utilizing agent-specific imaging with perfusion MRI in patients without cerebro- or cardio-vascular diseases suggested that TPI is also reliable in bolus kinetics of Levovist because it is not as depth dependent as other parameters, such as PI [6]. However, in in-vitro bolus kinetics using Optison, harmonic power Doppler imaging demonstrated no correlation of flow rate with TPI despite a close correlation with time to maximal enhancement [18]. TPI is influenced by various systemic and extracranial vascular factors such as heart rate, arrhythmia, heart ejection fraction, site of venous injection, and so on. Our TPI results showing no significant ACZ effects and positive correlations with TCD Vmax, are probably related to both factors. In order to avoid these factors, time to maximal enhancement [17,18] may be more suitable than TPI for quantification of brain tissue perfusion [4,6].

In conclusion, transcranial PHI allows quicker and easier evaluation of the increase contrast area size after ACZ that indicates vasoreactivity in the brain tissue. Combined use of transcranial PHI and TCD will be more useful for detailed analysis in vasoreactivity evaluation, utilizing ACZ, CO_2, and blood pressure, in both brain tissue and major cerebral arteries. The PHI vasoreactivity test will have clinical value in pathophysiological follow-up and therapeutic effectiveness determination in neurointensive care settings.

References

1. Postert T, Muhs A, Meves S, et al (1998) Transient response harmonic imaging: An ultrasound technique related to brain perfusion. Stroke 29:1901–1907
2. Seidel G, Algermissen C, Christoph A, et al (2000) Harmonic imaging of the human brain. Visualization of brain perfusion with ultrasound. Stroke 31:151–154
3. Shiogai T, Tsunezuka C, Ohara T, et al (2001) Clinical significance of transcranial contrast-enhanced harmonic perfusion imaging (HPI) as a quantitative method of measuring cerebral blood flow. Neurotraumatology 24:77–82 (in Japanese)
4. Eyding J, Krogias C, Wilkening W, et al (2003) Parameters of cerebral perfusion in phase-inversion harmonic imaging (PIHI) ultrasound examinations. Ultrasound Med Biol 29:1379–1385
5. Shiogai T, Koshimura M, Murata Y, et al (2003) Acetazolamide vasoreactivity evaluated by transcranial harmonic perfusion imaging: Relationship with transcranial Doppler sonography and dynamic CT. Acta Neurochir Suppl 86:57–62
6. Meves SH, Wilkening W, Thies T, et al (2002) Comparison between echo contrast agent-specific imaging modes and perfusion-weighted magnetic resonance imaging for the assessment of brain perfusion. Stroke 33:2433–2437
7. Meier P, Zierler LK (1954) On the theory of the indicator-dilution method for measurement of blood flow and volume. J Appl Physiol 6:731–744
8. Claassen L, Seidel G, Algermissen C (2001) Quantification of flow rates using harmonic grey-scale imaging and an ultrasound contrast agent: An in vitro and in vivo study. Ultrasound Med Biol 27:83–88
9. Seidel G, Meyer K, Algermissen C, et al (2001) Harmonic imaging of the brain parenchyma using a perfluorobutane-containing ultrasound contrast agent. Ultrasound Med Biol 27:915–918
10. Rim SJ, Leong-Poi H, Lindner JR, et al (2001) Quantification of cerebral perfusion with "Real-Time" contrast-enhanced ultrasound. Circulation 104:2582–2587
11. Meyer-Wiethe K, Cangur H, Seidel GU (2005) Comparison of different mathematical models to analyze diminution kinetics of ultrasound contrast enhancement in a flow phantom. Ultrasound Med Biol 31:93–98
12. Eyding J, Wilkening W, Krogias C, et al (2004) Validation of the depletion kinetic in semiquantitative ultrasonographic cerebral perfusion imaging using 2 different techniques of data acquisition. J Ultrasound Med 23:1035–1040
13. Shiogai T, Takayasu N, Mizuno T, et al (2004) Comparison of transcranial brain tissue perfusion images between ultraharmonic, second harmonic, and power harmonic imaging. Stroke 35:687–693
14. Henderson AR (1993) Assessing test accuracy and its clinical consequences: A primer for receiver operating characteristic curve analysis. Ann Clin Biochem 30 (Pt 6):521–539
15. Dahl A, Russell D, Rootwelt K, et al (1995) Cerebral vasoreactivity assessed with transcranial Doppler and regional cerebral blood flow measurements. Dose, serum concentration, and time course of the response to acetazolamide. Stroke 26:2302–2306

16. Hamann GF, Stoll M, Jost V, et al (1996) Time course of acetazolamide effect in normal persons. J Neuroimaging 6:29–31
17. Cangur H, Meyer-Wiethe K, Seidel G (2004) Comparison of flow parameters to analyse bolus kinetics of ultrasound contrast enhancement in a capillary flow model. Ultraschall Med 25:418–421
18. Ugolini P, Delouche A, Herment A, et al (2000) In vitro flow quantification with contrast power Doppler imaging. Ultrasound Med Biol 26:113–120

Neurointesive Care with Multimodal Monitoring

MITSURU HONDA[1] and YOSHIKATSU SEIKI[2]

Summary. Severe traumatic brain injury (TBI) is widely known to cause a dynamic change in cerebral blood flow (CBF). Especially, a decrease in CBF due to secondary brain insult has been reported. Currently it has widely been accepted that neurointensive care had a therapeutic benefit for severe brain TBI. Patients with severe TBI require a multidisciplinary approach to their management if a good outcome is to occur. For the safety of neurointensive care including mild hypothermia therapy, the control of many parameters from multimodal monitoring devices has a crucial importance. In patients with severe traumatic brain damage, we measured systemic arterial pressure (BP), intracranial pressure (ICP), jugular bulb oxygen saturation (SjO2), cardiac output (CO), systemic vessel resistance (SVR) and temperature of jugular vein (Temp. J). In addition, we periodically performed Xe-CT and perfusion CT, and created maps for CBF, mean transient time (MTT) and cerebral blood volume (CBV). These maps were utilized for evaluating cerebral circulation morphologically. Our university hospital's neurointensive care consists of evaluation of parameters from multimodal monitoring devices and normalization of ICP, cerebral circulation, SjO2 and systemic circulation with intubation, hyperventilation, control of body temperature, sedative agent and osmotic agent. Multimodal monitoring can be helpful for the optimal management and outcome improvement for the patients with severe TBI.

Key words. head injury, neurointensive care, computer monitoring system, multimodal monitoring, CBF

Head injury is a major cause of disability and death among young people. Neurointensive care has reduced the mortality and improved the outcome after severe traumatic brain over recent decades. The development of neuromonitoring in

[1] Critical Care Center, [2] Neurosurgery, Toho University Omori Medical Center, 6-11-1, Omori-nishi, Oota-ku, Tokyo 143-8541, Japan

neurointensive care units has enabled early detection of secondary complications and, thereby reduce secondary brain damage. Neurointensive care units have made advances with continuous neuromonitoring during the past decade. Improvements in neurointensive care have been predominantly in intensification and optimization of already established ways to monitor and treat patients. Primary brain damage is damage sustained immediately on direct impact. Secondary brain damage often results several days after from a secondary brain insult. Modern neurointensive care focus has been on prevention of secondary brain damage. Intracranially, as secondary brain damage advances, we see a rise in intracranial pressure, increased edema, vasospasm and seizure activity. Systemic manifestations of secondary brain damage are anoxia, hypercapnia, hypocapnia, hypotension, hyperthermia and hyperglycemia. In our study we collected the intracranial and systemic clinical effects of brain damage by using our NICU's advanced monitoring systems. By using this continuous neurointensive monitoring our institution's goal is to ultimately prevent and to establish effective treatment strategies for secondary brain insult.

Herein we introduce the monitoring systems of the neurointensive care unit in Toho University Hospital.

1 Bed Side Monitoring System

The multimodality monitoring we use continuously measures heart rate (HR), systemic arterial pressure (AP), central venous pressure (CVP), pulmonary artery pressure (PAP), end tidal CO2 (ETCO2), percutaneous artery blood oxygen saturation (SpO2), bladder temperature (Temp B), continuous cardiac output (CCO), continuous cardiac index (CCI) and mixed venous oxygen saturation (SvO2). In addition, we measure the intracranial pressure (ICP), jugular vein oxygen saturation (SjO2), jugular vein temperature (Temp J). We then input this data into a bedside personal computer with a digital signal and collect calculation parameters such as cerebral perfusion pressure (CPP), systemic vascular resistance index (SVRI), oxygen delivery index (DO2), oxygen consumption (VO2) and the oxygen extraction rate (O2ER). Both of these devices are separate and independent making simultaneous evaluation of blood flow and metabolic changes in both cerebral and systemic circulation not promblematic. To solve this practical problem, we have produced a new monitoring system using a personal computer system. In real time with system we can manage intaracranial and systemic changes immediately by a way of dual monitoring of brain damage and be able to set certain parameters (Fig. 1). There are many parameters provided by using these multimodality monitoring devices. It is important clinically to observe a trend change of parameters with time. Our monitoring system allows us by way of a trend graph to display trend changes on the same graph at the same time. A particular case where such monitoring is critical is in the case of hypothermia where the patient has constant fluctuations in parameters.

The beneficial effect of hypothermia treatment for the severe TBI patient has not been scientifically proven in humans, but in animal experimentation, a protective effect has been seen. Mild hypothermia induction to 34°C has been applied to patients with TBI and there are several case reports which show improvement in the outcome of severe TBI patients [1–3].

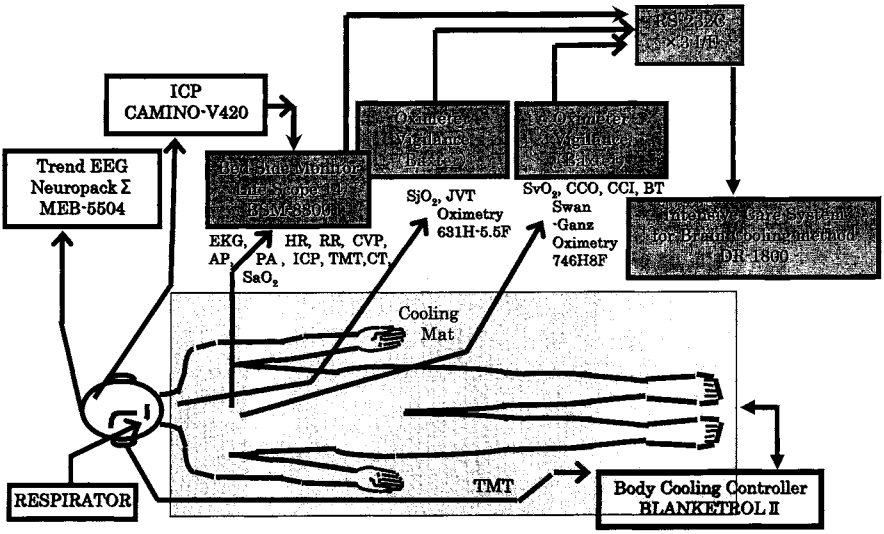


FIG. 1. Arrangement of our monitoring system for severe brain damage patients

While mild hypothermia protects the brain, this therapy has side effects, for example, infection, disturbance systemic circulation and hypokalemia. We illustrate a clinical cases using the Toho monitoring systems.

1.1 Case 1: 38 Year Old Male TBI

He sustained traumatic brain injury in severe traffic accident. On admission he was GCS4 (E1, V1, M2). Emergency CT demonstrated a right acute subdural hematoma and brain contusion. Emergency craniectomy was performed to remove the hematoma. After surgery, we initiated hypothermia therapy. As temperature of the jugular venous blood and mixed venous blood was lowered, a decrease in intracranial pressure was observed in the trend graph which correlated with the initiation of hypothermia therapy (Fig. 2). Blood pressure was kept constant during initiation, but, with decreasing temperature, SVRI rose and cardiac output deteriorated (Fig. 3). This case illustrates the disturbance in systemic circulation that takes place as shown by a decrease in CI which coincides with the initiation of hypothermia therapy. This disturbance of systemic circulation may contribute to secondary brain damage.

2 Image Monitoring

At present the CT is the standard imaging study to examine the traumatic brain. We performed this examination in order to evaluate intaracranial environment and repeated it as necessary during therapy. Severe TBI is widely known to cause a global decrease in cerebral blood flow (CBF) [4,5]. This decrease in cerebral blood flow can

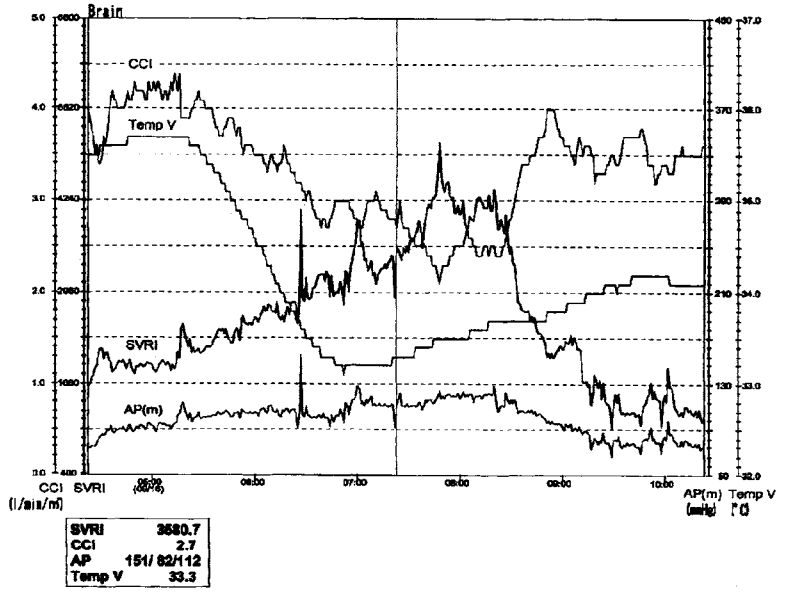


FIG. 2. Trend graph of parameters (SVRI, CCI, Temp V and ICP) upon initiation of hypothermia therapy. As temperature of mixed venous blood (*Temp V*) was lowered, a decrease in intracranial pressure (ICP) was observed in the trend graph

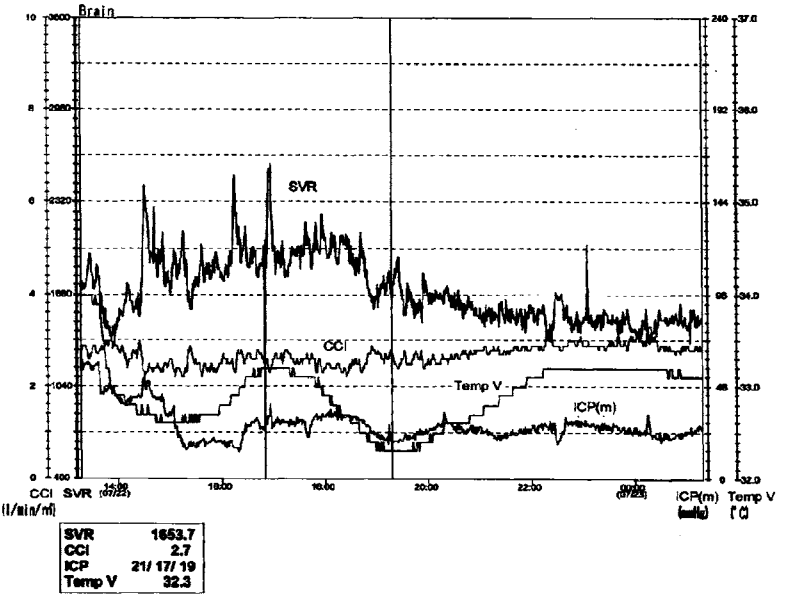


FIG. 3. Trend graph of parameters (SVRI, CCI, Temp V and AP) upon initiation of hypothermia therapy. Blood pressure (*AP*) was kept constant during initiation of hypothermia therapy, but, with decreasing temperatures (*Temp V*), systemic vascular resistance index (*SVRI*) roses, and cardiac output (*CCI*) deteriorated

TABLE 1. Relationship between grading on admission and parameters(CBF, MTT, CBV) (analysis of variance)

Outcome	CBF (ml/100 g/min)	MTT (s)	CBV (ml/100 g)
GR	32.2 ± 10.0	6.5 ± 0.9	3.4 ± 0.9
MD	28.7 ± 10.2	6.4 ± 0.9	2.9 ± 0.8
SD + VS	20.6 ± 9.5	7.6 ± 1.0	2.4 ± 0.9
D	19.3 ± 4.6	9.0 ± 1.4	2.6 ± 0.6
	($p = 0.065$)	($p < 0.01$)	($p = 0.181$)

cause ischemia and secondary brain damage. After a standard CT study, we performed perfusion CT study and Xe-CT study at the same time. It took only 30 min to evaluate the intra cranial circulation. We measured CBF by using Xe-CT and MTT by perfusion CT and calculated CBV by using AZ-7000W98 computer system. With these studies we created cerebral blood flow (CBF), mean transit time (MTT) and cerebral blood volume (CBV) maps. We were thus able to evaluate not only cerebral imaging but also CBF, MTT and CBV. In 24 patients with TBI, Xe-CT and perfusion CT were performed at the same time on either Day 1, 2, or 3. We measured CBF, MTT and CBV with this method. We evaluated the relationship between these findings and patient outcome. In addition, we were able to evaluate the effectiveness of various treatments.

Mean CBF values for normal subjects was 37.0 ± 4.2 ml/100 g/min. Mean MTT values for normal subjects was 5.7 ± 1.5 s. Mean CBV values for normal subjects was 7.6 ± 1.9 ml/100 g.

Summary of patients in this study: There were 2 females and 22 males, with a median age of 50.3 years (range 21–83). Median Glasgow Coma Scale before intubation and sedation was 6.3 points. Initial CT, performed within 1 h of the accident demonstrated brain contusions in 9 cases, diffuse axonal injury in 3 cases, subdural hematoma in 9 cases, and epidural hematoma in 3 cases. Of the 24 patients, 15 survived with good recovery or moderate disability, 2 survived with severe disability, 3 remained in a vegetative state and 4 died. We evaluated the relationship between CBF,MTT and CBV parameters and patient outcome. The values of CBF,MTT and CBV were 30.1 ± 9.9 ml/100 g/min, 6.5 ± 0.9 ml/100 g and 3.2 ± 0.9 s. in the favorable outcome group (GR + MD). The values of CBF,MTT and CBV were 20.1 ± 7.6 ml/100 g/min, 8.1 ± 1.3 ml/100 g and 2.4 ± 0.8 s in the unfavorable outcome group (SD + VS + D). There were significant differences between the parameters in the favorable group and unfavorable group (CBF $p < 0.01$, MTT $p < 0.01$, CBV $p < 0.05$). Analysis of variance and multiplex comparison in these groups was done. Analysis of variance showed significant differences in the parameter of MTT, and significant tendency in parameter of CBF with no significant differences noted in parameter of CBV (Table 1). We recognized significant differences in each group in multiplex comparison of MTT. We tried to predict the outcome by discriminant analysis using MTT and CBF. The probability was 78% (Fig. 4). The possibility that circulatory disturbance was the cause of secondary brain damage was suggested when we evaluated these parameters. Next, we illustrate a clinical example using CBF,MTT and CBV parameters.

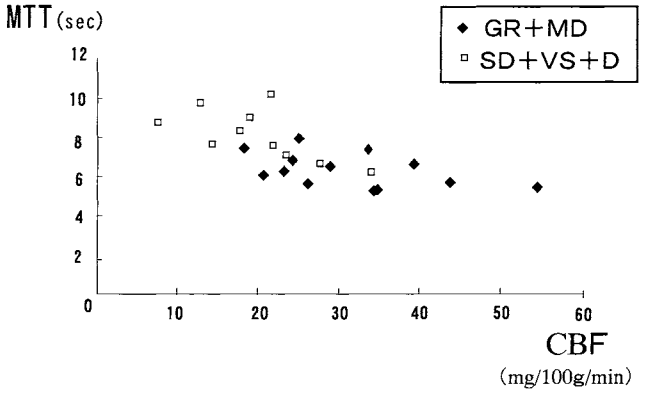


FIG. 4. Distribution map of CBF and MTT with traumatic brain injury. Discriminant analysis. Y = −0.0035CBF + 0.73MTT − 4.322

2.1 Case 2: 32 Year Old Male TBI

He sustained traumatic brain injury in a traffic accident while driving a motor cycle. On admission, he was GCS9 points (E2, V2, M5). Emergency CT demonstrated diffuse injury type II in Marshall's CT classification. He was intubated and hyperventilated (PaCO2, 35–40 mmHg). He recieved propofol infusion as sedation. An intraparenchymal probe for the ICP sensor was inserted because of compressed ventricles, and SjO2 catheter was inserted in juglar vein. ICP, cerebral perfusion pressure (CPP), intraarterial blood pressure, central venous pressure, oxygen saturation, and temperature were continuously monitored. The temperature of the jugular vein was kept between 35.5 and 36.5°C. Initial data of ICP and SjO2 were 20 mmHg and 54%, respectively. Xe-CT and perfusion CT were performed on Day 0. Values of CBF and MTT were each 33.9 ml/100 g/min and 6.6 s. On Day 1, CT demonstrated no remarkable change, but CBF values decreased on Day 1 compared to Day 0. On Day 1, SjO2 decreased to 46% and ICP was over 40 mmHg. A large right side craniectomy was performed for decompression. After surgery, CBF increased on Day 2 compared to Day 1. SjO2 increased and ICP decreased on Day 2. SjO2 increased from 46 to 63%, and ICP decreased from 40 to 20 mmHg. On Day 6 the patient's clinical data was good. On Day 7 sedation was discontinued and the patient was weaned from the ventilator. He had progressive recovery of consciousness and was classified in good recovery on discharge (Fig. 5).

In conclusion, these maps were utilized for evaluating cerebral circulation morphologically. Decision to perform surgery was not only taking into consideration ICP and SjO2 but also the trend changes on these maps. The neurointesive care consists of the following: constant evaluation of clonocal parameters from multimodal monitoring devices and the goal is to normalize ICP, cerebral circulation, SjO2 and systemic circulation. With intubation, hyperventilation, control of body temperature, and use of sedative and osmotic agents we are able to control body systems.

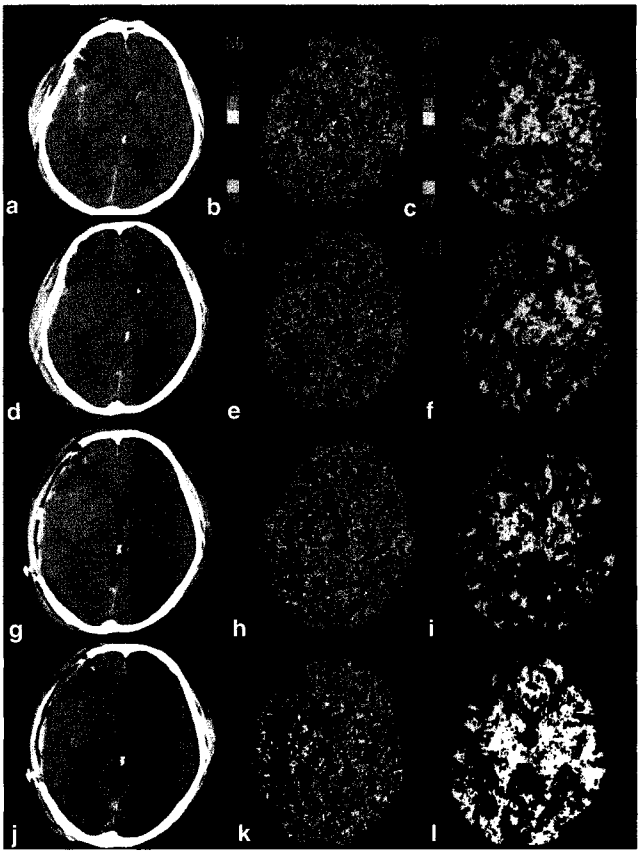


FIG. 5. CT (**a**),CBF map (**b**) and MTT map (**c**) on Day 0; CT (**d**),CBF map (**e**) and MTT map (**f**) on Day 1; CT (**g**),CBF map (**h**) and MTT map (**i**) on Day 2; CT (**j**),CBF map (**k**) and MTT map (**l**) on Day 6. CBF values decreased on Day 1 compared to Day 0. SjO2 decreased and ICP increased on Day 1 (SjO2 was 46%, ICP was over 40 mmHg) compared to Day 0 (SjO2 was 54%, ICP was under 20 mmHg). CBF values increased on Day 2 compared to Day 1. SjO2 increased and ICP decreased on Day 2 (SjO2 was 63%, ICP was under 20 mmHg) compared to on Day 1 (SjO2 was 46%, ICP was under 40 mmHg). CBF and MTT values were good on Day 6

Multimodal neurointensive care monitoring can be helpful for the optimal management of TBI and may improve outcome for patients with severe traumatic brain injury. Further study is needed to further define the clinical utility of neurointensive multimodal monitoring.

References

1. Marion DW, Obrist D, Carlier PM, et al (1993) The use of moderate therapeutic hypothermia for patients with severe head injuries: A preliminary report. J Neursurg 79:354–362

2. Shiozaki T, Sugimoto H, Taneda M, et al (1993) Effect of mild hypothermia on uncontrollable intracranial hypertension after severe head injury. J Neurosurg 79:363–368
3. Marion DW, Penrod LE, Kelsey SF, et al (1997) Treatment of traumatic brain injury with moderate hypothermia. N Engl J Med 336:540–546
4. Martin NA, Patwardhan RV, Alexander MJ, et al (1997) Characterization of cerebral hemodynamic phase following severe head trauma: Hypoperfusion, hyperemia, and vasospasm. J Neurosurg 87:9–19
5. Kelly DF, Martin NA, Kordenstain R, et al (1997) Cerebral blood flow as a predictor of outcome following traumatic brain injury. J Neurosurg 86:633–641

Right Median Nerve Electrical Stimulation for Coma Treatment—Recent Experience in Lithuania and the U.S.A.

Saulius Rocka[1], Egidijus Jarzemskas[1], Edwin Cooper[2,3], and Bryan Cooper[2]

Summary. Right median nerve electrical stimulation is known to be beneficial in management of patients with severe traumatic brain injury. Twelve comatose traumatic brain injured patients, admitted to Vilnius University Emergency Hospital, were enrolled in the "Vilnius Electrical Coma Treatment/Observation Research (VECTOR)" study. According to the consent of the relatives the patients were classified into the treatment group (7 patients, 2F, 5M) or control group (5 patients, 1F, 4M). In addition to the routine neurosurgical management, those in the treatment group received right median nerve stimulation daily. Results of the VECTOR study revealed significant increases in GCS (5.3 ± 1.4 *vs* 10.7 ± 3.5, $P = 0.005$) in treatment group, while control group results were lower (4.8 ± 0.4 *vs* 7.6 ± 3.8, $P = 0.18$). Analysis of brain CT scans showed that the patients without multiple contusions in the treatment group had a significantly better final GCS score (13.7 ± 1.5 *vs* 8.5 ± 2.9, $P = 0.03$). These data led to the conclusion that right median nerve electrical stimulation (RMNS) is effective in treating severe TBI patients without brainstem lesions.

Key words. traumatic brain injury, coma, median nerve, electrical stimulation

Everyone knows what consciousness is until he attempts of define it [1]. From the point of view of a psychologist, consciousness, from our natal day, is a teeming multiplicity of objects and relations. What we call simple sensations are results of discriminative attention, often pushed to a very high degree [1]. It is usually associated with the higher mental functions, such as feelings, attitudes and emotions, based on past memories and experience. From the viewpoint of physician, consciousness is the state of the patient's momentary awareness of self and environment and his responsiveness to external stimulation and inner need [2]. This is the more simple definition, what accents the voluntary response to the environment. The opposite of consciousness is unconsciousness: the state of unawareness of self and environment. Between these two extremes lie various conditions, which have indistinct limits. From

[1] Department of Neurosurgery, Vilnius University Emergency Hospital, Vilnius, Lithuania; [2] Department of Neurology, Virginia Commonwealth University, Richmond, VA, and [3] Department of Neurological Surgery, University of Virginia Health System, Charlottesville, VA, U.S.A.

the practical point of view of a physician, it is common to speak about the level of consciousness. The level of consciousness (LOS) is described in various scales, with the Glasgow Coma Scale (GCS) used most widely among the neurologists and neurosurgeons [3].

LOS can be affected by various conditions, which can be systemic (e.g. drug intoxication, severe metabolic disorders or infections) and focal (vascular disorders, tumors, abscess or traumatic brain injury). Taking into account the focal lesions, the core of the consciousness is located in the reticular formation of the upper brainstem, the ascending reticular activating system (ARAS) [4]. Primary brainstem damage is often associated with the patients who are in coma from the moment of injury and who do not have an intracranial expanding lesion [5]. But many patients stay in prolonged coma with no radiological evidence of changes in this site. There can be diffuse axonal injury or secondary insults after traumatic brain injury (TBI) [5]. The prolonged coma can be explained by the functional disorder of the upper brainstem reticular system. Can certain stimuli help the neural functions to recover?

Right median nerve electrical stimulation (RMNS) is known to be beneficial on various aspects of memory in patients with probable Alzheimer's disease [6,7]. RMNS shortens the time of awakening from deep coma in patients with TBI [8–10]. The median nerve serves as a peripheral gateway to the central nervous system (CNS). The concept of electrical stimulation in severe TBI is based on the hypothesis that electrical currents applied through peripheral routes, inducing electro-chemical propagated pulses, may reach central areas activating the neuroendocrine system to improve functioning after traumatic cerebral damage. It is proposed that the peripheral stimuli go to the ARAS in the brainstem connects with intralaminar nuclei of thalamus and then stimulates the cerebral cortex. The locus coeruleus (releasing norepinephrine), and the forebrain basal nucleus of Meynert (releasing acetylcholine), are also involved and stimulate the cortex, enhancing arousal. However, some other mechanisms may also be possible [8,11]. Neurosurgical researchers in Japan have documented increases in dopamine with right median nerve stimulation. In the acute phase after brain injury, comatose patients exhibit in the range of 20% increase in brain dopamine [12]. Increases in cerebral blood flow secondary to median nerve stimulation have been documented by Japanese researchers in acute and chronic cases of unconsciousness [11,13].

1 Experience with RMNS in the U.S.A.

Over the past dozen years there have been two small pilot studies comparing RMNS to sham stimulation for acute post traumatic coma patients in the Department of Neurosurgery at the University of Virginia, plus RMNS coma patients (without controls) at East Carolina University.

The time of coma was shorter in the treated groups at UVa than the controlled groups in the UVa Coma Stimulation Projects [8,9]. The neurophysiological effects of RMNS have been documented well at several centers in Asia using neuro-imaging, EEG, and spinal fluid assays [10–13].

Professor John Jane, the Chairman of Neurosurgery at the University of Virginia, with a long time wealth of neurotrauma research, summarized the challenge of explor-

ing median nerve stimulation. Dr. Jane wrote: "Very few things do work in this situation and if your techniques make any difference whatsoever, I think it should be well worth it" (J Jane, 1995, personal communication).

2 American Coma Cases

Two specific examples of teenagers in deep coma after closed head injury from a motor vehicle crashes (MVC) are demonstrated by videotape. One was treated on the East Coast (CI) and the other on the West Coast (JP) of the U.S.A. [14,15].

Both of these patients demonstrate the efficacy of starting the RMNS within the first few weeks following severe neurotrauma. Stimulation should not begin in the first couple of days however due to dopamine increases post injury [12].

CI, a 16 year old female, was involved in an MVC (1994) and sustained severe closed head injury. She suffered a basilar skull fracture, cerebrospinal fluid otorrhea, left facial fracture, and left pelvic fracture. CT scan revealed left internal capsule contusion, right cerebellar subarachnoid hemorrhage, and blood in the fourth ventricle. Decerebrate posturing was observed and she received a GCS of 4. She was briefly given electrical stimulation but intracranial pressures continued to rise. With her extremely poor prognosis, she was expected to die and was extubated. She breathed spontaneously and electrical stimulation was resumed to the right median nerve. Within 1 week of stimulation, she exhibited semi-purposeful movement of her right arm and leg and scored 7 on the GCS. After a total of 2 weeks of stimulation, she scored 10 on the GCS. This increase of 6 was consistent with the findings in the first UVa pilot project [8].

One month after the injury, CI followed simple commands. At 2 months post-injury CI could walk with assistance and read aloud. Two years later CI talked and walked well. She resumed dancing and driving. She completed high school and college with a "B" average. Now she is a recreation activity therapist at a large rest home [15].

JP was a 16-year-old girl in Southern California whose car was T-boned by a truck on the 24th of June of 2002. At the scene she had agonal respiration and was unresponsive (GCS 3). In the emergency room at a large community hospital her post-intubation coma score was GCS 4 on the day of the injury. The CT (computerized tomography) scan showed a large right putamen hemorrhage and small bleed in the mesencephalon. There was extensive shear injury in left fronto-temporal lobe and corpus callosum. Elevated intracranial pressure (ICP) was treated with Mannitol and hyperventilation.

Operations on the day of injury included exploratory laparotomy and splenectomy and ventriculostomy (tube in the left lateral ventricle with ICP monitoring). Later a tracheostomy and feeding tube were inserted. Follow-up brain CT scans on a daily basis at first showed progressive cerebral edema and increasing hemorrhage. Two days after the injury there was also a 7-millimeter midline shift. The small hemorrhage in the central mesencephalon was still present. By a week and a half post injury the swelling and hemorrhage stabilized on scans and then gradually decreased. By the 18th of July the ventricular system was slightly prominent. A week later there was cortical atrophy.

She remained in coma and was decerebrate/decorticate at four weeks post injury. Alternating bilateral median nerve electrical stimulation (six hours per day for each wrist median nerve stimulation site) was started at five weeks post injury. She remained in the intensive care unit for her entire hospitalization for two months after the injury. Two weeks after the start of the electrical stimulation she remained left hemiplegic, but could follow commands. After three weeks of electrical stimulation treatment JP could write, but could not speak. She was transferred to a rehabilitation unit eight weeks post injury.

At the unit she was able to speak in short sentences and also communicate by writing. Six weeks post injury she was able to walk with maximum support but remained left hemiplegic. Two months post injury she walked 250 feet with support. Three months post injury she had voluntary control of her left leg when walking. After three months of rehabilitation, she was transferred to a residential rehabilitation facility for an additional three months. She was discharged to home to the care of her family in early March of 2003, eight and a half months post injury brain injury. She continued to receive outpatient therapies [14].

Later in the spring of 2003 she graduated from high school on schedule with her class, less than one year post injury. The electrical stimulation program alternating between the two wrists for a total of twelve hours a day was done in the second month in the ICU and then on a less regular basis in the acute rehabilitation unit. She speaks in normal sentences with good conversation. Her voice tone is somewhat flat and there is mild dysarthria. She continues to do well in college, making B's. But the dense left hemiparesis remains. In a recent e-mail (2005) to the author, JP stated that she continues to do both land and pool therapies and was doing well. She walked approximately 25 min independently using parallel bars, but for longer distances she uses a power wheelchair.

3 Discussion

In previous studies it was noted that the slope of the timeline of partial neurological recovery is inversely related to the interval of time from the injury to the startup of RMNS [8,9]. The quality of the functional outcome is influenced by the severity of the neurotrauma as diagnosed on early CT scans [16].

The objectives of the VECTOR study were to confirm the effectiveness of afferent brain stimulation in the treatment of coma patients and to correlate the outcome with the clinical and radiological data.

4 Material and Methods of the Lithuanian Vector Coma Project

Twelve comatose TBI patients, admitted to the Neurosurgery Service of the Vilnius University Emergency Hospital, were enrolled in the VECTOR study (Table 1). Inclusion criteria required post resuscitation GCS score from 4 to 8, age 16 years or more and written consent of the relatives. All patients with implanted pacemakers or defibrillators, spinal cord injury or pregnancy were excluded.

TABLE 1. Description of the patients

No	Age	Gender	Type of trauma	GCS on admission	Group
1	41	Male	Fall	6	Control
2	23	Male	Motor vehicle accident	5	Treatment
3	34	Male	Assault	4	Control
4	28	Male	Motor vehicle accident	5	Treatment
5	20	Male	Not known	4	Treatment
6	44	Female	Motor vehicle accident	4	Treatment
7	52	Male	Assault	4	Treatment
8	25	Male	Not known	3	Control
9	54	Male	Not known	5	Control
10	24	Female	Motor vehicle accident	4	Treatment
11	22	Male	Assault	5	Treatment
12	40	Female	Not known	5	Control

According to the consent of the relatives (whether consent for treatment or control) the patients were enrolled in the treatment group or the control group. RMNS was started in the treatment group. No difference in routine management of head injury was allowed in both groups. The same criteria were used to collect data in both the electrically treated and control (no electrical stimulation) groups. These data included demographics, time and type of trauma, initial CT scan evaluation, best GCS score daily, maximal ICP daily, management (surgery, osmotics, ventilation, adrenergics), daily pupil size and response. The outcome, based on Glasgow Outcome Scale (GOS) was evaluated on day 21 and after 1 year.

The treatment group consisted of 7 patients: 2 female (F) (28.6%), 5 male (M) (71.4%), average age 30.43 ± 12.5 years (range 20–52 years). The average inclusion time in the study was 167.3 hours (range 30 h–16 days). Most of them had survived a motor vehicle crash (MVC) (4 persons, 57.1%), others sustained TBI during assault (2 persons, 28.6%). For one patient, the cause of TBI remained unknown (14.3%). The average GCS score on admission was 4.4 ± 0.5 (range 4–5), and 5.3 ± 1.4 (range 4–7) on the first day of treatment. Initial CT scan revealed 3 patients (42.9%) with subdural hematoma, one with epidural, and one with traumatic intracerebral hematoma (14.3% respectively). More than half of the patients (4 persons, 57.1%) had multiple contusions diagnosed. One patient (14.3%) was in coma without any changes in the initial CT scan. Most of the patients had midline shift up to 0.5 cm (4, 57.1%), two—up to 1.5 cm (18.6%), and one more than 1.5 cm (14.3%). Basal cisterns were opened in 2 patients (28.6%), semi-opened in 3 (42.9%) and closed in 2 CT scans (28.6%). All of the patients in this group given standard neurosurgical treatment plus received RMNS.

The control group contained 5 patients: 1 F (20%), 4 M (80%), average age 38.8 ± 10.6 years (range 25–54 years). The average inclusion time in the study was 22.0 h (range 18–24 h). The cause of TBI in most of the patients in this group was unknown (3 patients, 60.0%), one patient sustained traumatic brain injury during the assault (20.0%), and one patient was comatose after a fall (20.0%). The average GCS score on admission was 4.6 ± 1.1 (range 3–6), and 4.8 ± 0.4 (range 4–5) post-resuscitation. Initial CT scan revealed 4 patients (80.0%) with subdural hematoma, 2 (40.0%) with epidural, and one with traumatic intracerebral hematoma (20.0%). Only one of these

patients (20.0%) had multiple contusions diagnosed. One patient (20.0%) was in coma without any changes in the initial CT scan. Most of the patients had midline shift 0.5–1.5 cm (3, 60.0%), one—no shift (20.0%), and one more than 1.5 cm (20.0%). Basal cisterns were opened in 1 patient (20.0%), semi-opened in 2 (40.0%) and closed in 2 CT scans (40.0%). All of the control group patients received routine neurosurgical treatment without RMNS.

The device that was used to provide electrical impulses was the FDA approved Focus Plus 300 PV neuromuscular stimulator (manufactured by the Empi Corporation, distributed by the ORMED Company, Freiburg, Germany). This device has multiple settings that allow various parameters for trains of electrical pulses. The electrical stimulation is delivered by two lubricated rubber electrodes contained inside a plastic cuff. This is applied to the volar surface of the right wrist to stimulate the right median nerve. Stimulation was delivered by trains of 300 microsecond pulses 35/second at 15–20 milliamps (as tolerated). The stimulation was given intermittently, 20 s on, and 50 s off. This regimen was found effective in previous studies [8–10]. The treatment was done for 8 h daily for 3 weeks if the patient remained in coma. RMNS was discontinued when the patient regained consciousness (GCS more than 8).

Data was analyzed using a standard Microsoft Excel worksheet and Statistica for Windows (Ver. 5.0, StatSoft Inc., U.S.A.) statistical package. Descriptive data are reported as mean (± standard deviation). The two-tailed unpaired t test was used to define the difference in means. A difference was considered significant if a P value 0.05 or less was calculated.

5 Results

Comparison of the treatment and control groups showed no significant differences between the groups in age and gender. Although the GCS score on admission was higher in control group (4.4 ± 0.5 *vs* 4.6 ± 1.1, $P = 0.77$), it become lower after the resuscitation (5.3 ± 1.4 *vs* 4.8 ± 0.4, $P = 0.4$). Initial CT scan analysis revealed the main intracranial lesion in both groups as subdural hematomas ($42.9 \pm 16.0\%$ in treatment group *vs* $80.0 \pm 35.6\%$ in controls, $P = 0.34$), but the treatment group had more persons with multiple contusions ($57.1 \pm 21.4\%$ *vs* $20.0 \pm 8.7\%$, $P = 0.1$). However more persons in the treatment group had no or minimal (0–0.5 cm) midline shift ($57.1 \pm 21.4\%$ *vs* $20.0 \pm 8.7\%$, $P = 0.1$). Persons in the control group had midline shifts between 0.5 and 1.5 cm ($28.6 \pm 10.6\%$ *vs* $60.0 \pm 26.6\%$, $P = 0.3$). No marked differences were observed in the basal cisterns.

As was mentioned, the GCS score in the start of the study was higher in the treatment group (5.3 ± 1.4 *vs* 4.8 ± 0.4, $P = 0.4$) and stayed higher in the end of the study (10.7 ± 3.5 *vs* 7.6 ± 3.8, $P = 0.2$). These differences were not statistically significant. However, the treatment group inside it demonstrated significantly better GCS score in the end of the study (5.3 ± 1.4 *vs* 10.7 ± 3.5, $P = 0.005$) than the control group does (4.8 ± 0.4 *vs* 7.6 ± 3.8, $P = 0.18$). Inside the treatment group, 5 patients (71.4%) regained consciousness, while only 2 patients (40.0%) did well in the control group. This difference is not statistically significant ($P = 0.3$). But the small number of patients might influence the proportions and statistics. Surprisingly, it took a longer time for the electrically stimulated patients to regain consciousness than the control patients

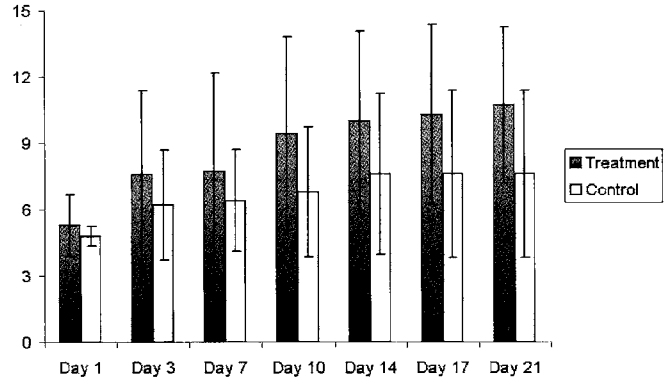


FIG. 1. Distribution of GCS in time

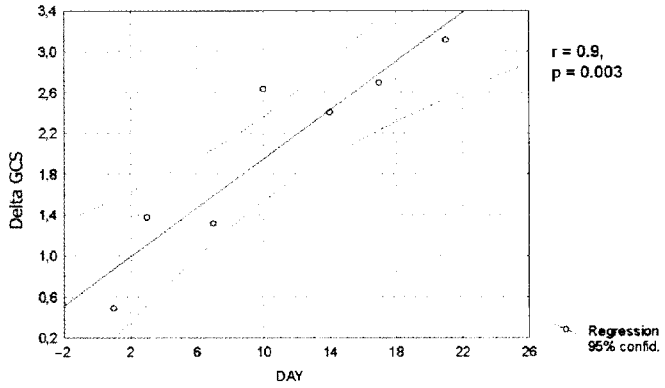


FIG. 2. Correlation of differences in GCS with time

(7.4 ± 5.6 days *vs* 5.5 ± 3.5 days, $P = 0.6$). But most of the controls does not regain the consciousness at all.

The total difference in the GCS was not significantly higher in the treatment group (5.0 ± 3.3 *vs* 2.8 ± 3.7, $P = 0.3$). But looking at the distribution in time, a better trend was always demonstrated in electrically stimulated persons (Fig. 1). Moreover, the positive correlation of the differences between the control and treatment groups was also significant ($r = 0.9$, $P = 0.003$, Fig. 2).

When looking at the CT scans, major attention was drawn to the multiple contusions (primary brainstem lesion was not separated from the hemisphere lesions). All the patients (stimulated and un- stimulated) were pooled and distributed into groups without contusions (1st group, 7 patients, 4 from the control group and 3 form the treatment group) and with diagnosed contusions (2nd group, 5 patients, 1 person from control group and 4 from the treatment group). Initial GCS scores in both groups were similar (5.3 ± 0.8 in the 1st group *vs* 5.0 ± 1.4 in the 2nd, $P = 0.7$). Five patients (71.4%) in the 1st group (no contusions) regained consciousness. Only two (40.0%)

did well in the second group with contusions ($P = 0.3$). The final GCS score was better in the "no contusions" group (10.4 ± 4.4 *vs* 8.0 ± 2.7, $P = 0.3$). The patients without diagnosed multiple contusions had a better outcome also (2.9 ± 0.7 *vs* 2.4 ± 0.5, $P = 0.2$). Despite the better trends, these differences were not significant statistically. However, looking to the multiple contusions inside the treatment group (4 patients without contusions and 3 patients with contusions), the significantly better final GCS ($13.7p = \pm 1.5$ *vs* 8.5 ± 2.9, $P = 0.03$) score was observed between those who had no contusions and were electrically stimulated. All the patients in this group regained consciousness (100% *vs* 50%, $P = 0.4$). They had better outcomes also (3.3 ± 0.6 *vs* 2.5 ± 0.6, $P = 0.1$), but these differences were found not to be significant statistically.

The day 21 outcome was better in the treatment group (2.9 ± 0.7 *vs* 2.4 ± 0.5, $P = 0.2$). The favorable outcome is defined as Glasgow Outcome Scale 4 = moderate disability or 5 = good outcome. On day 21 a favorable was obtained in one person in the treatment group (14.3%, $P = 0.006$ *vs* controls).

The late (1 year outcome) emphasized the better outcome. There were 2 patients (28.6%) in a good/moderate group, while no one of the patients in the control group reached this good result. As it was expected, the was an increase in the death rate—3 patients (42.9%) were dead after one year in the treatment group and 3 patients (75%) between the controls. One patient (20%) from the control group was lost in the evaluation of late outcomes.

6 Discussion

The patients in the electrical treatment group in this study had a significantly better final score of the GCS and better GOS. One treated coma patient achieved a favorable outcome at three weeks and there were two patients with the favorable outcome after one year. Usually, positive trends in the right median nerve stimulated group were observed. But this was not commonly proved by statistical significance, possibly under the influence of small number of patients. The previous studies demonstrated better GCS score and GOS outcome [8,9,15]. The observations made in American studies correspond to the results in this Lithuanian study.

The correlation of the post-resuscitation GCS score and outcome is well established in the literature [17–19]. The average initial GCS in this study was 5.3 ± 1.4 in the treatment group and 4.8 ± 0.4 between the controls. Good or moderate discharge outcome on initial GCS 4–5 varies from 14.4% to 29.3% [17]. This VECTOR study produced 14.3% favorable outcome in the control group and 0% in controls. As noted, this may the consequence of the small number of tested coma patients. Surprisingly, no deaths were observed in both groups when evaluating early outcome. Death rate in the initial GCS 4–5 group in the literature amounts to 40.2–55.9% [17]. However late outcomes restored equilibrium, but the death rate was again lower in the treatment group (42.9% treatment group and 75.0% controls). Such difference between early and late outcomes can be explained by patient selection: a post-resuscitation score of GCS 3 (no movement to noxious stimulation) did not satisfy inclusion criteria and those patients were excluded.

A normal CT scan at the time of admission after severe head injury is associated with a lower mortality and better functional recovery than for patients whose scans

are abnormal, even among patients with an initial GCS score of 3 or 4 [20]. In this study only 2 patients (one in each group) had no changes in the initial CT scan. On the other hand, the presence of a surgically significant intracranial hematoma is associated with a worsened prognosis [21,22]. The majority of the patients in this study had intracranial hemorrhage. Intracerebral contusions, especially involving brainstem, are often associated with a poor outcome [23].

Those right median nerve electrically stimulated patients in the study, who had no contusions on the CT scan, had a significantly better final GCS score than those who had contusions. This leads to the assumption that lower outcome scores in this study might be associated with the initial traumatic brain tissue changes. The final GCS score in the control group was not significantly higher in patients with or without contusions.

Therefore electrical stimulation might be the stimulus which helps to activate the brainstem reticular formation. This underline mechanism leads to arousal of the brain, and a quicker and better awakening from coma. Early awakening, like early mobilization after any type of surgery, yields better objective scores. The final result can be a better functional neurological outcome for electrically treated coma patients.

7 Conclusions

Right median nerve stimulation is effective in treating severe TBI patients without brainstem lesions. More patients are needed to increase the statistical and scientific power of the study.

Acknowledgements. We want to thank the U.S. Embassy in Vilnius for the grant for the VECTOR study.

References

1. James W (1890) The principles of psychology. Henry Colt & Co., New York
2. Adams R, Victor M, Ropper A (1997) Principles of neurology, 6th edn. McGraw-Hill, New York
3. Jennett B, Teasdale G (1981) Management of head injuries. Davis Company, Philadelphia, PA, pp 77–93
4. Berry M, Standring S, Bannister L (1995) Reticular formation of the brainstem. In: Williams PL (ed.) Gray's Anatomy, 38th edn. Churchill Livingstone, New York
5. Graham D, Gennarelli T (2000) Pathology of brain damage after head injury. In: Cooper PR, Golfinos J (eds) Head injury, 4th edn. McGraw-Hill, New York
6. Scherder E, Bouma A, Steen L (1998) Effects of "isolated" transcutaneous electrical nerve stimulation on memory and affective behavior in patients with probable Alzheimer's disease. Biol Psychiatry 43:417–424
7. Scherder E, Bouma A (1999) Effects of transcutaneous electrical nerve stimulation on memory and behavior in Alzheimer's disease may be stage-dependent. Biol Psychiatry 45:743–749
8. Cooper J, Jane J, Alves W (1999) Brain Inj 13:261–267
9. Cooper E, Cooper J (2003) Electrical treatment of coma via the median nerve. Acta Neurosurgica 87:7–10
10. Liu J, Wang C, Chou I, et al (2003) Regaining consciousness for prolonged comatose patients with right median nerve stimulation. Acta Neurosurgica 87:11–14

11. Yokoyama T, Kamei Y, Kanno T (1996) Right median nerve stimulation for comatose patients. Soc Treat Coma 5:117–125
12. Moriya T, Sakurai A, Hayashi N, et al (1998) New therapeutic strategies for patients with unconsciousness and neurological deficits in acute stage with median nerve stimulation. Soc Treat Coma 7:65–69
13. Hirata Y, Murakami M, Ushio U (2002) The analysis of regional cerebral blood flow changes by median nerve stimulation on xenon CT in patients with cerebrovascular disease at the chronic stage. Soc Treat Coma 11:33–37
14. Cooper E, Cooper J (2003) Electrical treatment of comatose teenagers via the median nerve. Acta Neurochir (Wien) 145:1140–1141
15. Cooper E, Kanno T (2005) Electrical treatment of coma. In: Carrion J, von Wild K, Zitnay G (eds) Brain injury treatment: theories and practices. Psychology Press, New York
16. Kido D, Cox C, Hamill R, et al (1992) Traumatic brain injuries: Predictive usefulness of CT. Radiology 182:777–781
17. Marshall LF, Gautille T, Klauber MR, et al (1991) The outcome of severe closed head injury. J Neurosurg 75:S28–S36
18. Andrews BT (2000) Prognosis in severe head injury. In: Cooper PR, Golfinos JG (eds) Head injury, 4th edn. McGraw-Hill, New York, pp 355–364
19. Ghajar J (2000) Traumatic brain injury. Lancet 356:923–929
20. Lobato RD, Sarabia R, Rivas JJ, et al (1986) Normal computerized tomography scans in severe head injury: Prognostic and clinical implications. J Neurosurg 65:784–789
21. Wardlaw JM, Easton VJ, Statham P (2002) Whish CT features help predict outcome after head injury? J Neurol Neurosurg Psychiatry 72:188–192
22. Choi SC, Muizelaar JP, Barnes TY, et al (1991) Prediction tree for severely head-injured patients. J Neurosurg 75:251–255
23. Mittl RL, Grossman RI, Hiehle JF, et al (1994) Prevalence of MR evidence of diffuse axonal injury in patients with mild head injury and normal CT findings. AJNR Am J Neuroradiol 15:1583–1589

Management of Patients with Traumatic Brain Injury: Our Strategy

Hirosuke Fujisawa, Eiichi Suehiro, Hiroshi Yoneda, and Michiyasu Suzuki

Summary. Over the past 10 years, we have been managing patients with severe head injury on the basis of guidelines published in the U.S.A., Europe and Japan. Here we report our strategy for managing patients with severe head injury, including hypothermia therapy. Intracranial hematomas are evacuated, and external decompression is performed. Cerebrospinal fluid (CSF) drainage and/or implantation of an intracranial pressure (ICP) sensor is also performed. For patients with diffuse axonal injury (DAI), a CSF drainage catheter and/or ICP sensor is inserted. In patients for whom hypothermia therapy is appropriate, brain and body temperatures are maintained at 32–33°C for 3–8 days. Intracranial pressure, temperatures of the brain, jugular vein, bladder and pulmonary artery, and O_2 saturation in the jugular vein are measured continuously. Intensive care using various monitoring tools is necessary for patient management. Systemic circulation is monitored using a Swan-Ganz catheter. Blood gas, blood cells, and chemical data are frequently checked and abnormal values are corrected without delay. The purpose of this management approach is to control ICP and to inhibit secondary damage that can spread from the primary site of injury. In DAI, so-called secondary axotomy should be prevented.

Key words. traumatic brain injury, secondary injury, management, intensive care, hypothermia

1 Introduction

Over the past 10 years, we have been managing patients with severe head injury on the basis of guidelines published in the U.S.A., Europe and Japan. Immediate treatment of shock and hypoxia and early correction of abnormal values of blood

Department of Neurosurgery, Clinical Neuroscience, Yamaguchi University School of Medicine, 1-1-1 Minamikogushi, Ube, Yamaguchi 755-8505, Japan

parameters are necessary, and for this purpose, completion of a system for emergency medicine is essential. We began to use brain hypothermia therapy in 1994, and at the same time, we also began a policy of managing the body temperature of patients. On the basis of our experience, we report our recent strategy for managing patients with severe head injury.

2 Clinical Materials and Methods

Our standard management involves evacuation of intracerebral hematoma, cerebral contusion, acute subdural hematoma, and decompressive craniectomy. In patients with diffuse axonal injury (DAI), cerebrospinal fluid (CSF) drainage is performed. If this is impossible, an intracranial pressure (ICP) sensor (Camino ICP sensor, U.S.A.) is implanted. Figure 1 shows an example of the management. This is 61-year-old female with a Glasgow Coma Scale (GCS) score of 7. She showed bilateral mydriasis on admission. A subdural hematoma on the left side was removed through a burr hole, and then contusional hematoma was evacuated. Decompressive craniectomy was performed. Then a catheter for CSF drainage and ICP measurement was inserted. As such a drain often becomes occluded, an ICP sensor was also inserted.

Many parameters are monitored sequentially. Intracranial pressure (ICP), cerebral perfusion pressure (CPP), temperatures of the brain, jugular vein, bladder and pulmonary artery, and O_2 saturation in the artery (SaO_2) and jugular vein ($SjvO_2$) are measured continuously. Systemic circulation is monitored using a Swan-Ganz

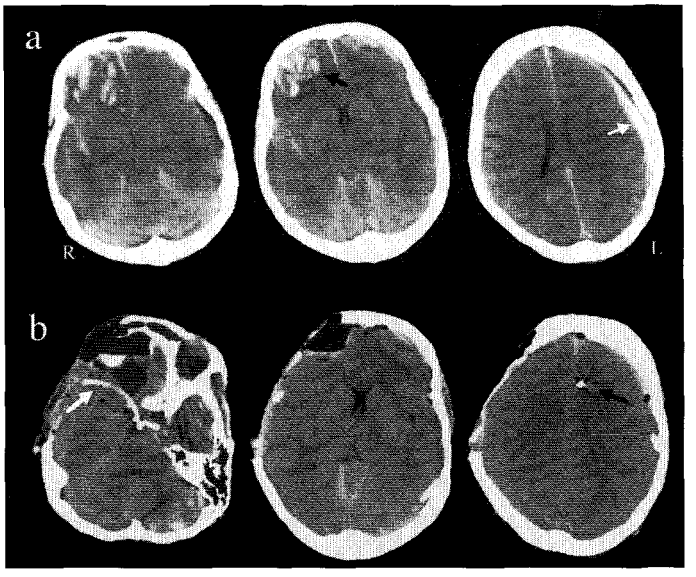


FIG. 1. **a** Preoperative CT scan. *White arrow*: acute subdural hematoma. *Black arrow*: contusional hematoma. **b** Postoperative CT scan. *White arrow*: catheter for CSF drainage. *Black arrow*: ICP sensor

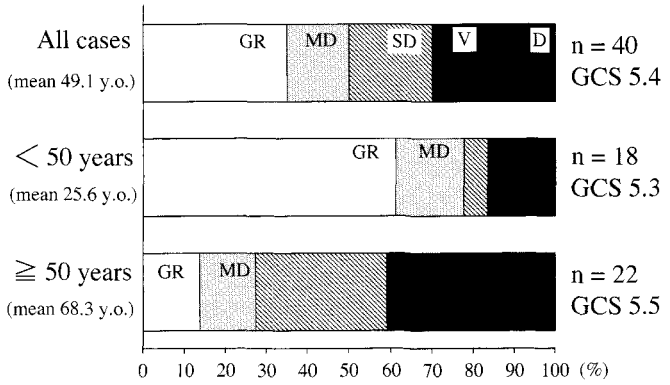


FIG. 2. Outcomes for patients in the recent five years. In all cases, the proportion of favorable outcomes, that is good recovery and moderate disability on the Glasgow Outcome Scale, was 50%. Among patients below 50 years of age, favorable outcomes were seen in 78%. Among patients aged 50 years and over, favorable outcomes were seen in 27%

catheter. Blood gas, blood cells and chemical data are checked frequently. Physiological and chemical parameters each have target values (i.e. systolic blood pressure > 120 mmHg, mean arterial blood pressure > 90 mmHg, PaO_2 > 100 mmHg, $PaCO_2$ = 30–35 mmHg, SaO_2 > 95%, intracranial pressure < 20 mmHg, cerebral perfusion pressure > 70 mmHg, temperature 37°C, hematocrit > 30–35%, hemoglobin > 10 g/dl, platelets > 100,000/l, albumin ≥ 3 g/dl, osmotic pressure = 280–320 mOs/l, blood sugar = 100–150 mg/dl, arterial pH = 7.40 ± 0.05). Most patients are kept in a normo- or hypervolemic state, as monitored using the Swan-Ganz catheter. These treatments are based on the Japan Society of Neurotraumatology guidelines for treatment and management of patients with severe head injury edited [1].

Basically, we induce moderate hypothermia in patients with a Glasgow Coma Scale score of 8 and below. In patients for whom hypothermia therapy is appropriate, brain and body temperatures are maintained at 32–33°C for 3–8 days. Mild hypothermia (34°C–35°C) is induced according to the patient's condition. Even if hypothermia is not induced, the brain temperature is kept below 37°C. Hypothermia is induced as soon as possible using a cooling blanket. To prevent bacterial infections, antibiotics are used. More importantly, brushing and washing of the mouth and nose using diluted povidone-iodine is performed at least four times a day.

We focused on the recent five years, and analyzed the outcomes in this period. Forty patients with a GCS score of 8 and below were studied.

3 Results

In all cases, the proportion of favorable outcomes, that is good recovery (GR) and moderate disability (MD) on the Glasgow Outcome Scale, was 50% (Fig. 2). Among patients below 50 years of age, favorable outcomes were seen in 78%, which seems satisfactory. However, among patients aged 50 years and over, favorable outcomes were seen in 27%. The outcomes for patients with abnormal pupil reactions are shown in

TABLE 1. Ratio of favorable outcomes for patients with abnormal pupils

Abnormal pupils	<50 years	≥50 years
Unilateral ($n = 16$)	5/7 (71.4%) (GR 4)	2/9 (22.2%) (GR 1)
Bilateral ($n = 11$)	2/4 (50.0%) (GR 1)	2/7 (28.6%) (GR 1)

Favorable outcomes: good recovery (GR) and moderate disability (MD) on Glasgow Outcome Scale.

TABLE 2. Outcomes for patients with diffuse axonal injury

Case	Age	Gender	Cause of injury	GCS	Abnormal pupil	Hypothermia	GOS
1	42	Male	Traffic accident	5	–	–	MD
2	22	Male	Traffic accident	6	Bilateral	+	GR
3	18	Male	Traffic accident	7	Unilateral	+	GR
4	49	Male	Traffic accident	3	Bilateral	+	MD
5	17	Male	Traffic accident	6	Unilateral	+	GR

GCS, Glasgow Coma Scale score; GOS, Glasgow Outcome Scale; MD, moderately disabled; GR, good recovery.

Table 1. The ratio of favorable outcomes was considerable for patients younger than 50 years. The outcomes for patients with DAI are shown in Table 2. Three cases were GR, and 2 were MD. However, all five patients were younger than 50 years.

4 Discussion

The aim of treatment of patients with traumatic brain injury should be to reduce such secondary injuries, which occur not only around the site of primary injury, but also in remote areas. One of the most advantageous effects of hypothermia is to inhibit brain edema and reduce ICP. However, the final goal of the treatment, and therefore the aim of hypothermia and temperature management, is to reduce such secondary injuries. Hypothermia protects the brain by inhibiting brain edema and the diffusion of neurotoxic substances from the site of primary injury. Previously, using a rat contusion model, we have shown that the concentrations of glutamate increased significantly after production of the contusion [2]. Furthermore, autoradiography after intravenous ^{14}C-glutamate injection demonstrated diffusion of the ^{14}C-glutamate from the vascular compartment to the contused area of the brain. This suggests that neurotoxic substances, including glutamate of vascular origin, enter the brain as a result of mechanical stress. In other studies using a rat model of intracerebral glutamate infusion via a microdialysis probe, we demonstrated that glutamate-induced brain damage was reduced by mild hypothermia (32°C) and was increased by hyperthermia (40°C), proving that brain temperature has an important role in excitotoxic processes [3]. Furthermore, when glutamate solution containing ^{14}C-sucrose, used as a marker of the extracellular space, was infused into the brain, the volume of ^{14}C-sucrose diffusion increased as the brain temperature increased. These findings suggest that hypothermia inhibits the diffusion of neurotoxic substances from the site of primary injury.

In DAI, primary axotomy occurs one hour after injury [4]. Axonal swelling and loss of axonal transport occurs 2 to 6h after injury, leading to secondary axotomy. Hypothermia may affect the processes leading to secondary axotomy.

The present study showed that the prognosis for older patients was much worse than that for younger patients. Although some problems with hypothermia therapy have been pointed out, there is currently no practical and better alternative to this therapy. Some type of breakthrough is needed.

In conclusion, the aim of management for patients with traumatic brain injury should be to reduce the extent of secondary injuries that occur not only around the site of primary injury, but also in remote areas. The aim of management for patients with DAI should be to inhibit secondary axotomy. Since severe traumatic brain injury is a systemic disease that includes abnormalities of the circulatory, respiratory and digestive systems, full equipment for intensive care and considerable manpower are necessary.

References

1. Japan Society of Neurotraumatology (2001) Guidelines for treatment and management of patients with severe head injury. Igaku-shoin, Tokyo
2. Koizumi H, Fujisawa H, Ito H, et al (1997) Effects of mild hypothermia on cerebral blood flow-independent changes in cortical extracellular levels of amino acids following contusion trauma in the rat. Brain Res 747:304–312
3. Suehiro E, Fujisawa H, Ito H, et al (1999) Brain temperature modifies glutamate neurotoxicity in vivo. J Neurotrauma 16:285–297
4. Maxwell WL, Povlishock JT, Graham DI (1997) A mechanistic analysis of nondisruptive axonal injury: A review. J Neurotrauma 14:419–440

Clinical Features in the Patients with "Platform Accident" in Tokyo

Yoji Node[1], Tomonori Tamaki[1], and Akira Teramoto[2]

Summary. There are many railways and underground like a net of meshes in Tokyo. This accident may be considered to be very unique to big cities. We defined the injury at platform in the station as "platform accident". The number of the patients was 96 (mean age: 44 years). Pattern of injury was classified into three groups: contact injury with train at platform (A), injury by falling from the platform without train injury (B), and with train injury (C). Carelessness was the main cause of injury in the Group A, drinking in the Group B, and suicide in the Group C. The highest incidence of the injury was head and neck in the Group A and B, and limbs and pelvis in the Group C. Mean Glasgow coma scale in each group was 9.1, 11.7, and 6.9, respectively. The mortality rate was 50%, 4%, and 61%, respectively. Although the patients in the Group C seemed to be severely injured compared to those in the Group A and B, it was indicated that, in the patients excluding suicide, the extent of injury had a tendency to be rather mild and their mortality was relatively low.

Key words. platform, station, head injury, multiple injury

1 Introduction

Tokyo is one of big cities in the world, and there is many railways and underground like a net of meshes. So, we have occasionally experience the injured patients at platform in the station. This accident may be considered very unique to big cities, and we defined the injury at platform as "platform accident". The purpose of this study is to describe the clinical features of the patients with platform accident.

Department of Neurosurgery, [1]Nippon Medical School, Tama Nagayama Hospital, 1-7-1 Nagayama, Tama, Tokyo 206-8512, [2]Nippon Medical School, Sendagi, Bunkyo-ku, Tokyo, Japan

2 Materials and Methods

Platform accident in the station was classified into three different groups by pattern of injury as follows. Group A had a contact injury with train at the platform. Group B had an injury by falling from the platform, but patients had no injury by train. And Group C had an injury by falling from the platform, and train injured patients.

We had experienced 96 patients with platform accident for 11 years. Seventy-one were male and 25 were female, and the mean age of them was 44 years with a range of 2 months to 85 years. A two months old baby was a victim who fell from the platform and injured by train with his mother, because his mother tried suicide with him. His mother died, but this baby could fortunately survive in spite of multiple damage of extremities.

3 Results

Table 1 demonstrated the summary of the patients with platform accident. About 60% of the patients were in the Group C, that is, these patients fell down from the platform and were injured by train. The male/female ratio was 4 to 1 in the Group A, 5 to 1 in the Group B. But in the Group C, this ratio is about 2 to 1. The reason for increase the number of female in the Group C is due to the increase of the number of female with suicide or attempted suicide.

Cause of injury was summarized in Table 2. Suicide or attempted suicide occupied as much as 40% of cause of injury. Drinking and carelessness occupied 25%, respectively. The main cause of injury was very different in each group. Carelessness was the

TABLE 1. Type of injury of the platform accident in the station

Type of injury	Group	No. of cases (male:female)
Injury at platform	A	16 (13:3)
Falling from the platform		
Without injury by train	B	23 (19:4)
With injury by train	C	57 (39:18)
Total		96 (71:25)

TABLE 2. Cause of injury of the patients with platform accident

Cause of injury	Group			Total
	A	B	C	
Suicide	0	0	28	28
Attempted suicide	1	3	8	12
Drinking	2	14	9	25
Carelessness	10	3	11	24
Fight	2	2	0	4
Illness	1	1	1	3
Total	16	23	57	96

TABLE 3. Incidence of injury (%) at the parts of the body in the patients with platform accident

Region	Group			Total
	A	B	C	
Head and neck	69	61	58	63
Chest	31	17	54	42
Abdomen	0	0	9	5
Limbs and pelvis	25	35	88	67

TABLE 4. Number of the patients with/without head injury in platform accident

Region of injury	Group			Total
	A	B	C	
Head alone	8	9	0	17
Except for head	5	9	27	41
Both head and others	3	5	30	38
Total	16	23	57	96

TABLE 5. Prognosis, mortality rate, and main cause of death in the patients with platform accident

	A	B	C	Total
Survivors	8	22	22	52
Non-survivors	8	1	35	44
Mortality rate (%)	50	4	61	46
Main Cause of death				
Direct brain damage	5	1	2	8
Multiple injury	3	0	33	36

main cause of injury in the Group A, drinking was frequent in the Group B, and suicide or attempted suicide was main cause of injury in the Group C.

The incidence of injury at the parts of body was indicated in Table 3. In the Group A and B, the main region of injury was head and neck. Meanwhile, in the Group C, the incidence of injury of limbs and pelvis was very high (88%), but in head and neck or chest, that exceeded only 50%, respectively. On the other hand, with respect to the abdominal injury, the proportion of them was extremely low in each group.

Table 4 demonstrated the number of the patients with/without head injury in the platform accident. Concerning the head injury, the incidence of head injury alone was 50% in the Group A and 40% in the Group B. But, in the Group C, we didn't experience the patients with head injury alone.

Prognosis, mortality rate, and main cause of death were shown in Table 5. In our series, overall mortality rate was 46%. The mortality rare was 50% in the Group A, 61% in the Group C. On the other hand, in the Group B, that was only 4%, and which was extremely low compared to that in Group A and B. Meanwhile, in the Group A,

TABLE 6. Mean GCS and ISS on admission in the patients with platform accident

	Group			Total
	A	B	C	
Mean GCS				
Survivors	13.6	12.0	12.4	12.5
Non-survivors	4.9	5	3.1	3.6
Total	9.1	11.7	6.9	8.4
Mean ISS				
Survivors	7.6	12.5	11.2	11.3
Non-survivors	26.8	16	36.5	34.2
Total	17.7	12.6	26.5	21.7

GSS, Glasgow Coma Scale; ISS, injury severity score.

TABLE 7. Cause of injury and mortality rate in the Group C[a]

	Suicide	Others
No. of patients	28	29
Mortality rate (%)	100	24.1

[a] Falling from the platform with injury by train.

over 60% of the patients died of direct brain damage. In the Group B, only one patient died of traumatic intracerebral hemorrhage. This patient had a history of thrombocytopenia, and which was considered to take part in the cause of death. In the Group C, direct brain damage did not play an important part in the main cause of death, and almost all patients died of multiple injuries.

Mean Glasgow coma scale (GCS) [1] and mean injury severity score (GCS) [2] on admission were demonstrated in Table 6. The mean GCS was 9.1 in the Group A, 11.7 in the Group B, 6.9 in the Group C, respectively. In survivors, mean GCS was similar in each group. On the other hand, in non-survivors, mean GCS on admission was 4.9 in the Group A, 5 in the Group B, and 3.1 in the Group C. Non-survivors in the Group C exhibited extremely severe state on admission. On the other hand, the mean ISS was high In the Group C (26.5 in total) compared with that of Group A and B. In the Group C, mean ISS of non-survivors was very high (36.5) compared with that in the Group A and B, 26.8 and 16, respectively. But, in the survival group, mean ISS was not so different in each group. These results were suggested that the extent of injury was very different between survivors and non-survivors in the Group C.

As to the Group C, high mortality rate had revealed, that was over 60%. In these 57 patients, the number of the patients with suicide was 28, and that without suicide was 29. In 29 non-suicide cases, only 7 cases died. This mortality rate was very low, that was 24% (Table 7). This result suggested that the extent of injury in the survived patients who fell from platform with injury by train be considered to be relatively mild.

4 Discussion

As mentioned above, we defined the injury at platform in the station as "platform accident". This paper might be considered to be the first report as to this kind of injury.

In the platform accident in the station, type of injury was classified into 3 groups, which were Group A, B and C. The main cause of injury was different in each group. Carelessness was most frequent in the Group A, and drinking in the Group B, and suicide in the Group C, respectively. The highest incidence of injury was also different in each group. That was head and neck in the Group A and B, and limbs and pelvis in the Group C.

The mortality rate was over 50% in the Group A and C, however, in the Group B, that is falling down from the platform without injury by train, the mortality rate of this group was only 4%. So, in this group, extent of injury had a tendency to be mild, and the prognosis was very excellent. The main cause of death was direct brain damage in the Group A, and multiple injury in the Group C.

Finally, although the patients in the Group C seemed to be severely injured compared to those in the Group A and B, it is indicated that the patients excluding suicide, the extent of injury had a tendency to be rather mild and their mortality rate was relatively low.

References

1. Teasdale G, Jannett B (1974) Assessment of coma and impaired consciousness: A practical scale. Lanset II:81–84
2. Baker SP, O'Neill B, Haddon W, et al (1974) The injury severity score: A method for describing patients with multiple injuries and evaluating emergency care. J Trauma 14:197–196

Screening for Hypopituitarism Following Traumatic Brain Injury (TBI)

GIANLUCA AIMARETTI[1], CLAUDIO PERINO[2], SILVIA ROVERE[1], GIULIA CHIARA CROCE[1], KRISTIAN PERRONE[2], ROBERTO RAGO[2], and EZIO GHIGO[1]

Summary. Results of recent and ongoing studies have made it clear that traumatic brain injury (TBI) poses substantial risks to pituitary function, perhaps even greater than previously believed. Patients with sequelae of TBI should be screened, both prospectively and retrospectively, for isolated and multiple pituitary deficits. It is well known that patients with "classical" hypopituitarism do benefit from hormonal replacement therapy. It has been suggested that patients with hypopituitarism following TBI may benefit as well with appropriate hormonal supplements if necessary. Patients with TBI-induced hypopituitarism might initially receive critical replacement therapy, such as anti-diuretic hormone (ADH), glucocorticoid and thyroid hormones. Gonadal and rhGH replacement therapy should also be introduced at a later stage, if these deficiencies are demonstrated and subsequently reconfirmed. The signs and symptoms of post-traumatic hypopituitarism may be masked by what has been assumed are merely the cognitive and behavioural sequelae of TBI. By increasing awareness among all physicians about the risks of TBI-induced endocrinopathy and about the need for appropriate endocrinological testing, it may be possible to improve quality of life and enhance the rehabilitation outcome for these patients. In most instances, these patients are first seen and treated by neurointensivists, trauma surgeons and neurosurgeons, and subsequently by rehabilitation physicians. All these specialists must be aware about the risks of hypopituitarism, so that they may determine which patients are appropriate candidates for hypopituitary screening. Additionally, endocrinologists and internists must be educated about TBI-induced endocrinopathies, and encouraged to actively share their expertise with other physicians. Prospects for rehabilitation of patients with TBI-induced hypopituitarism may be enhanced by appropriate neuroendocrine diagnostic approach, leading to correct hormonal therapies. Further exploration of this possibility requires active collaboration between divisions of endocrinology and rehabilitation medicine, at the local level, to perform a screening of pituitary function in patients following TBI.

Key words. hypopituitarism, traumatic brain injury, hormonal replacement therapy

[1] Division of Endocrinology and Metabolism, Department of Internal Medicine, University of Turin, and [2] Presidio Sanitario Ausiliatrice—Fondazione Don Carlo Gnocchi Onlus, Turin, Italy

1 Introduction

The first report of anterior pituitary dysfunction as a result of traumatic brain injury was published in 1918 [1]. Subsequent reviews and case reports identified additional instances of hypopituitarism following head injury [2–4]. In particular, the special article by Benvenga and coworkers [5] included 367 historical patients with TBI-induced hypopituitarism, together with new data of 15 patients from their own centre, and alerted many endocrinologists on the problem. The Authors found that in most cases (71%) hypopituitarism was diagnosed within one year of injury, although occasionally the diagnosis was not made for more than 20 years after the injury. Indeed, there are reports of patients with total, multiple, or isolated hypopituitarism whose clinical data revealed a history of previous TBI, many years before the endocrinological diagnosis, but the patients themselves did not recall their brain injury without prompting, or the assistance of a friend or family member [5].

2 Post TBI Hypopituitarism: Review of Recent Scientific Literature

Already in 1986, Edwards and Clark reviewed the topic of post-traumatic hypopituitarism, finding that the typical patient was a young adult male with a severe case of previous head trauma, presenting endocrinological symptoms, months to years after an accident. These patients would often have reported temporary or permanent diabetes insipidus, as well as weight loss, fatigue, vertigo, loss of libido, and impotence. Cases of hypopituitarism had been ascribed to depression, or the "post-concussion syndrome", and often inappropriate treatment and rehabilitation had been advised. Following these observations, it was recommended that patients with major head injury (defined by post-traumatic amnesia greater than 24 h), and in particular those with fractures of the base of the skull or diabetes insipidus, should be closely monitored for symptoms and signs of endocrine dysfunction, and appropriate dynamic pituitary-function tests should be performed [4].

In 2000 and 2001 Kelly and Lieberman first found high prevalence of anterior pituitary dysfunction, in patients who had had a history of previous moderate and severe TBI [6,7]. The incidence of growth hormone (GH) deficiency (15%) and low cortisol levels (46%) are striking, and may have important implication for patients' health, sense of well-being, and rehabilitation potential [6,7] In his paper Kelly emphasized how also the occurrence of subarachnoid haemorrhage (SAH) poses a high risk for hypopituitarism [6]. This picture was more recently confirmed by other studies in both TBI and SAH [8–15]. The percentage of hypopituitaric patients after TBI or SAH generally varied between 20 and 80 %. These studies were generally retrospective, some testing patients who had had brain injury more than one year before, others testing patients early after TBI or SAH [6,7,9–13,15]. All Authors emphasized the clinical relevance of brain injury-induced anterior pituitary dysfunction, and hypothesized that appropriate hormonal replacement would provide peculiar improvement also to the post-traumatic syndrome and benefit to the recovery of patients [8].

The high risk for brain-induced hypopituitarism, and particularly for anterior pituitary dysfunction, was clear also in our studies (performed under the auspices of the

Italian Society of Endocrinology), where we tested the pituitary function 3 and 12 months after the pathological event, in 2 groups of patients (one after TBI, the other after SAH) [14]. It has to be emphasized that this study was planned as a prospective one, aiming to define pituitary function at least one year after the brain injuries. In other words, we wished to clarify whether pituitary deficiencies or normal pituitary function, recorded at 3 months, would improve or worsen, respectively, at 12 months post-onset. To this goal, in a multicenter study and in a considerable number of patients who suffered TBI ($n = 100$) or SAH ($n = 40$), we evaluated the pituitary function at 3 and 12 months after the pathological events. The results of these prospective studies confirm the high and similar risk for anterior pituitary dysfunction in both TBI and SAH patients, demonstrating that an early diagnosis of severe total hypopituitarism is always confirmed at long term after the brain injury. Moreover, these data indicate that pituitary function in brain injured patients may sometimes improve over time, in case of isolated deficits. On the other hand, normal pituitary function at 3 months may, although rarely, become impaired 12 months after the injury. Thus, these studies definitely provide the clinical evidence that brain injured patients must undergo neuro-endocrine evaluations and follow-up over time, in order to monitor pituitary function and eventually provide appropriate hormonal replacement therapy.

3 Possible Pathogenesis of Post TBI Hypopituitarism

The pathogenesis of brain injury-induced anterior pituitary dysfunction is still far to be elucidated. However, it has to be considered that very old studies in patients who had had fatal traumatic brain injury demonstrated that various degree of pituitary haemorrhagic infarction was present in more than 70% of patients [16,17] while hypothalamic microhaemorrages were present in at least 40% of cases [18]. Pituitary stalk lesion has been demonstrated unlikely to be a major cause of brain injury-induced hypopituitarism [17]. It is noteworthy that hypopituitarism is not associated to the severity of the neurological status after the brain injury [6,13,14]. In other words, the initial Glasgow Coma Scale (GCS) does not, in our study and other studies, correlate with the occurrence and/or severity of hypopituitarism. In authopsy studies, the existence of a clear post-traumatic hypothalamus-pituitary lesions well explains the high incidence of hypopituitarism. On the other hand, in clinical trials these types of lesions may leave open the possibility that anterior pituitary dysfunction, recorded early after brain injury, would further progress or, alternatively, that would be transient, so that a recovery of pituitary function is allowed over time. Overall, our best estimate at present is that a combination of necrotic, hypoxic, ischaemic and shearing/tearing lesions at the hypothalamus and/or the pituitary, may be the physiopathological basis of post-TBI endocrinopaties, and that this may leave open some possibility of clinical improvement.

References

1. Cyran E (1918) Hypophysenschädigung durch Schädelbasisfraktur. Dtsch Med Wochenschr 44:1261
2. Altman R, Pruzanski W (1961) Post-traumatic hypopituitarism. Ann Intern Med 55:149–154

3. Kusunagi H, Kogure K, Teramoto A (2000) Pituitary insufficiency after penetrating injury to the sella turcica. J Nippon Med Sch 67:130–133
4. Edwards OM, Clark JDA (1986) Post-traumatic hypopituitarism: Six cases and a review of the literature. Medicine 65:281–290
5. Benvenga S, Campenni A, Ruggeri RM, et al (2000) Hypopituitarism secondary to head trauma. J Clin Endocrinol Metab 85:1353–1361
6. Kelly DF, Gonzalo IT, Cohan P, et al (2000) Hypopituitarism following traumatic brain injury and aneurysmal subarachnoid hemorrhage: A preliminary report. J Neurosurg 93:743–752
7. Lieberman SA, Oberoi AL, Gilkison CR, et al (2001) Prevalence of neuroendocrine dysfunction in patients recovering from traumatic brain injury. J Clin Endocrinol Metab 86:2752–2756
8. Casanueva FF, Ghigo E, Popovic V (2004) Hypopituitarism following traumatic brain injury (TBI): A guideline decalogue. Athens TBI and Hypopituitarism Study Group. J Endocrinol Invest 27:793–795
9. De Marinis L, Mancini A, Valle D, et al (1999) Hypothalamic derangement in traumatized patients: Growth hormone (GH) and prolactin response to thyrotrophin-releasing hormone and GH-releasing hormone. Clin Endocrinol (Oxf) 50:741–747
10. Agha A, Rogers B, Mylotte D, et al (2004) Neuroendocrine dysfunction in the acute phase of traumatic brain injury. Clin Endocrinol (Oxf) 60:584–591
11. Agha A, Rogers B, Sherlock M, et al (2004) Anterior pituitary dysfunction in survivors of traumatic brain injury. J Clin Endocrinol Metab 89:4929–4936
12. Kreitschmann-Andermahr I, Hoff C, Saller B, et al (2004) Prevalence of pituitary deficiency in patients after aneurysmal subarachnoid hemorrhage. J Clin Endocrinol Metab 89:4986–4992
13. Bondanelli M, De Marinis L, Ambrosio MR, et al (2004) Occurrence of pituitary dysfunction following traumatic brain injury. J Neurotrauma 21:685–696
14. Aimaretti G, Ambrosio MR, Di Somma C, et al (2004) Traumatic brain injury and subarachnoid haemorrhage are conditions at high risk for hypopituitarism: Screening study at 3 months after the brain injury. Clin Endocrinol (Oxf) 61:320–326
15. Brandt L, Saveland H, Valdemarsson S, et al (2004) Fatigue after aneurysmal subarachnoid hemorrhage evaluated by pituitary function and 3D-CBF. Acta Neurol Scand 109:91–96
16. Daniel PM, Prichard MML, Triep CS (1959) Traumatic infarction of the anterior lobe of the pituitary gland. Lancet 2:927–930
17. Kornblum RN, Fisher RS (1969) Pituitary lesions in craniocerebral injuries. Arch Pathol 88:242–248
18. Crompton MR (1971) Hypothalamic lesions following closed head injury. Brain 94:165–172

Development of the New Coma Scale: Emergency Coma Scale (ECS)

Masahiro Wakasugi[1], Hiroshi Okudera[1], Tomio Ohta[2], Takeshi Asahi[1], Akihiko Igawa[1], and Daisuke Tange[1]

Summary. Development of the new coma scale, Emergency Coma Scale, is presented. The task force for development of Emergency Coma Scale (ECS) originated from an ad-hoc committee meeting held in cooperation with the Japanese Congress on Neurosurgical Emergencies and the Japan Neurosurgical Emergency Society. ECS is the combination of advantages of Glasgow Coma Scale (GCS) and Japan Coma Scale (JCS). Design of an open trial comparing ECS with GCS and original JCS to prove accuracy of ECS in the emergency room will be presented.

Key words. coma scale, emergency, ECS

1 Introduction

Coma scale is fundamental to assess the patients of disturbed consciousness. Without using coma scales, it is hard to evaluate and discuss about not faced patients. Objective indicator of impaired consciousness is vital to compare treatment results of coma patients with other institution.

In 1974, famous Glasgow Coma Scale (GCS) was proposed by Teasdale and Jennett [1], and since then it prevailed all over the world. Curiously enough, In the same year, Japan Coma Scale (JCS) was proposed by Ohta, and now JCS is very popular and widely used in Japan [2]. By using those coma scales, we are able to assess altered mental status patients adequately, and it remains a component of many algorithms used for field triage decision. Though GCS and JCS are extensively used in emergency department settings, they have their own advantages and disadvantages for acute phase of disturbed consciousness [3]. Thus we are developing the new coma scale "Emergency Coma Scale (ECS)", which is the combination of advantages of GCS and JCS.

In this report, we introduce Emergency Coma Scale; ECS, and present the design of an open trial to prove accuracy of ECS in the emergency department.

[1] Department of Emergency & Disaster Medicine, Faculty of Medicine, University of Toyama, 2630 Sugitani, Toyama 930-0194, and [2] Chairman, Japan Emergency Coma Scale (ECS) Society, Japan

TABLE 1. Japan Coma Scale

One-digit code: The patient is awake and
JCS-1: almost fully conscious
JCS-2: disoriented
JCS-3: unable to recall name and date of birth
Two-digit code: The patient is able to be aroused by
JCS-10: speech
JCS-20: painful stimuli
JCS-30: only repeated painful stimuli
Three-digit code: The patient is not aroused by painful stimuli, but responds with
JCS-100: localizing
JCS-200: slight movement
JCS-300: none

TABLE 2. Glasgow Coma Scale

Eye opening	
Spontaneous	4
To speech	3
To pain	2
None	1
Verbal response	
Oriented	5
Confused conversation	4
Inappropriate words	3
Incomprehensible sound	2
None	1
Motor response	
Obey commands	6
Localizes pain	5
Normal flexion (withdrawal)	4
Abnormal flexion (decorticate)	3
Extension (decerebrate)	2
None	1

2 Japan Coma Scale; JCS (Table 1)

JCS is divided into three major levels, according to the grade of *One-digit code*: the patients is arousal, *Two-digit code*: the patients can be aroused, and *Three-digit code*: the patients is not arousable. Each level is further divided into three levels, then ten grades as a total, including 0 in clear consciousnessIn. JCS has advantages as below, that JCS consists of one axis scale, eye opening with a blink is used as a substitute of arousal. That means that we can select one score at one level and we can judge whether the patients condition deteriorate or not. Furthermore, JCS is so simple and easy to memorize, that it can be assessed easily by co-medical staffs. In Japan, it is widely used, especially by pre-hospital emergency life guard [4].

Meanwhile, JCS has some drawbacks. The term "arousal" is occasionally difficult to understand its meaning correctly. As compared with GCS, JCS might be insufficient

TABLE 3. Emergency Coma Scale

One-digit code: The patients open their eyes, speak, and/or behave spontaneously (awake), and
ECS-1: oriented
ECS-2: disoriented
Two-digit code: The patients can open their eyes, speak, and/or behave (aroused) by
ECS-10: speech
ECS-20: painful stimuli
Three-digit code: The patients can neither open their eyes, nor speak by painful stimuli (not aroused), but respond with
ECS-100L: localizing
ECS-100W: withdrawal movement
ECS-200F: decorticated posture
ECS-200E: decerebrated posture
ECS-300: none

to evaluate severe grades, in GCS the motor level is divided into six grades, but in JCS the level of severe grades is divided only into three grades.

3 Glasgow Coma Scale; GCS (Table 2)

GCS is a 3-component clinical scoring system. The components as follows, Eye opening, Verbal response and Motor response, are scored independently, and now, differ from original scoring, usually expressed as total score of three components from three to fifteen in thirteen grades.

The GCS has prevailed all over the world as a ubiquitous neurologic tool. On the other hand, GCS is not simple enough to quickly learn and recall. It has multiple axis and so multiple score in one level, there are 120 combinations at 13 levels, and three components can not rarely be summed up [5]. Further more, GCS can not to be used in cases, such as in patients who are intubated or tracheostomy because verbal response is hardly to take. For the layman, it is difficult to determine the difference between normal flexion and abnormal flexion.

4 Emergency Coma Scale; ECS (Table 3)

We thought that coma scale in the acute stage should be simple and straightforward on one axis [6]. Then, the task force for ECS, originated from an ad-hoc committee meeting held in cooperation with the Japanese Congress on Neurosurgical Emergencies and the Japan Neurosurgical Emergency Society, proposed ECS as the new coma scale in an acute stage of disturbed consciousness.

The ECS has some features as below, that ECS represents the best mix of the advantages of GCS and JCS, suggests the intracranial situation on one axis in 3 stages like a traffic signal and that is simple and easy to memorize. Thus ECS can be used in any situation, by anyone.

Three stages are expressed as follows;

One-digit code: The patients open their eyes, speak, and/or behave spontaneously (awake), *Two-digit code*: The patients can open their eyes, speak, and/or behave

(aroused) by, and *Three-digit code*: The patients can neither open their eyes, nor speak by painful stimuli (not aroused).

Three-digit code is divided to five grades like motor components of GCS, so ECS could estimate depth of impaired consciousness more particularly than JCS. The application of ECS is simple and easy to memorize without employing difficult terms like "arousal", and always can be assessed by the same score among the medical stuff or layman.

Further more it can be used in any situations, such as in patients who are intubated, tracheostomy, or in aphasics because ECS is not respond to verbal response.

5 Multicenter Trial

To evaluate accuracy of ECS, we designed an open trial that comparing ECS with GCS and JCS in the emergency department. The purpose of this study is to reveal the conformity and validity of ECS.

The first study is designed to evaluate the conformity of ECS by different estimators. We prepared some case studies of clinical situations, by visual material and writing scenario, that patients of disturbed consciousness such as neurotrauma, stroke and so on. Then varied job category estimators, such as paramedics, nurses and doctors, concurrently assessed the same case and corrected scores of 3-form coma scales (ECS, GCS, JCS). We will evaluate the dispersion of corrected scores by different estimators.

Next study is designed to evaluate the validity of the ECS as a predictive tool of patients prognosis.

We will assess patients coma scales with diachronic and check outcomes that we thought to be clinically relevant to clinicians caring for patients in the acute phase of disturbed consciousness. Outcome measures, that we selected, are as following, intubations in emergency departments, neurosurgical interventions and patients mortality. Correlation between ECS and those outcomes will be analyzed.

We presented the new coma scale, used in an acute stage, Emergency Coma Scale and projet of a multicenter clinical trial of ECS. We will notify the results of this study in no distant future and we hope ECS would be widely used in evaluation of acute phase disturbed consciousness.

References

1. Teasdale G, Jennett B (1974) Assessment of coma and impaired consciousness: A practical scale. Lancet 2:81–84
2. Okudera H, Hara H, Kuroyanagi T, et al (1986) [CT findings of acute death following severe head injury.] Jpn J Acute Med 10:863–869
3. Kobayashi S, Okudera H (1994) Early manegement of head injury in Japan. In: Merry G, Atkinson L (eds) ICRAN 94, vol. 1. NSA, Australia, pp 17–19
4. Takeuchi E, Ohta T (1997) [Grading of level of consciousness.] Nippon Rinsho 55 (Suppl 1):315–317 (in Japanese)
5. Ohta T (2003) Transition of the depth of consciousness disturbance and its perspectives —from Japan Coma Scale to Emergency Coma Scale. J Jpn Congr Neurol Emerg 16:1–4
6. Ohta T (2005) Phenomenological aspects of consciousness—its disturbance in acute and chronic stages. Acta Neurochir Suppl 93:191–193

Pre-hospital Care for Patients with Severe Traumatic Brain Injury: A Retrospective Analysis of JAPAN Neurotrauma Data Bank

Akira Satoh[1], Hiroshi Nakamura[2], and The Japan Neurotrauma Databank Committee[3] (The Japan Society of Neurotraumatology and The Japanese Council of Traffic Science)

Summary. The purpose of this report is to clarify the present situation of pre-tertiary hospital (PTHp) medical care for those with severe TBI by investigating retrospectively the data provided from the Japan Neurotrauma Data Bank (JNTDB).

One thousand and two cases registered in JNTDB were used for the study. In cases receiving PTHp medical care at first-aid or secondary hospital, 5.1% were in shock state with blood pressure below 60 mmHg on admission. Incidence of shock was 3.5% in those admitted directly from accident scene. Regarding respiratory care, only 21.9% of cases in coma with PTHp medical care were intubated, although physiological data and outcome at discharge are not different in groups with or without endotracheal intubation. As a conclusion, further improvement of PTHp medical care at primary or secondary hospitals is required at least regarding circulatory-respiratory managements.

Key words. traumatic brain injury, prehospital care, emergency medicine, neurotrauma databank, physiological parameters

1 Introduction

The basis of emergency medical system in Japan consists of a cooperation of medical institutions, which are categorised as the first-aid or primary, the secondary and the tertiary emergency hospitals, with public emergency rescue bureaus. Patients with traumatic brain injury (TBI) are usually treated at the first-aid or the secondary institutions and then transferred to the tertiary ones in case that further specific treat-

[1] Department of Neurosurgery, and Department of Emergency Medicine, Saitama Medical School, 38 Moro-hongo, Moroyama-cho, Iruma-gun, Saitama 350-0495, [2] Department of Neurosurgery, Chiba Emergency Medical Center, Isobe, Hanamigawa-ku, Chiba City, Chiba, [3] Department of Neurosurgery, The Jikei University School of Medicine, Nishi-Shinbashi, Minato-ku, Tokyo, Japan

ment is required. Some are directly brought into the tertiary ones, if emergency rescue personnel judge that an advanced neurosurgical care is required immediately.

Pertinent pre-hospital medical care for severely ill patients has become one of the most important problems to be dealt with by physicians working in the field of emergency medicine in Japan [1,2], especially in the last decade, as well as being so in most of other countries [3,4]. During this period of time, the system of pre-hospital care provided by ambulance rescue staffs in Japan has been changed in many ways, and at the same time, emergency physicians' participation in this field has been by far the much increased [1,2]. In consequence, pre-hospital care for those with TBI has also been changing in many ways [1–10]. In order to constitute the most effective system, precise evaluation of the present status by analyzing data obtained from multiple trauma centers being involved in treatment for patients with severely ill TBI must be necessary. The major purpose of this report is to clarify the present situation of pre-tertiary hospital (PTHp) medical care for those with severe TBI, mainly from the viewpoint of physiological data on admission to the tertiary trauma centers.

2 Materials and Methods

The data base used in this study was provided from Japan Neurotrauma Data Bank (JNTDB) by courtesy of the concerning committee of the Japan Society of Neurotraumatology and the Japanese Council of Traffic Science.

One thousand and two cases that showed consciousness impairment with GCS 8 or less at least once at acute stage of JNTDB were studied. Because there were numbers of data defect, cases without data entry in each studied item were omitted from analysis. Studied group is 48.2 ± 23.5 years old in average and contains 754 male and 248 female. As physiological parameters on admission, arterial blood pressure (BP), pulse rate (PR), arterial carbon dioxide tension (PCO_2) and arterial oxygen tension (PO_2) were used. Data obtained from patients who were directly brought into tertiary emergency institutions form accident scene (DIR) were compared with those obtained from patients transferred from first-aid or secondary emergency ones after primary medical care for trauma (MED). Statistical analysis was made by Student *t*-test, Chi-square test and Mann-Whitney test.

3 Results

Mean BP was 139.4 ± 40.7 and 139.5 ± 41.7 in DIR and MED groups respectively. PR was 94.2 ± 27.4 beats per minutes (b/min) and 91.7 ± 22.6, PCO_2 was 41.6 ± 16.0 and 39.4 ± 11.4 and PO_2 was 161.2 ± 131.7 and 204.6 ± 163.3 in DIR or MED group respectively. Statistically significant difference is present as to PCO_2 and PO_2 level between these two groups (Table 1).

Distribution of BP on admission in DIR or MED group reveals that 77.5% of the former and 73.8% of the latter are with BP within the range of 80 to 180 mmHg, which can be regarded as physiological and relatively safe range, although some are actually in shock or extremely hypertensive state in both groups (Fig. 1, top). As to PR on admission in both groups, 74.6% of DIR and 71.9% of MED are in a physiological range from 60 to 120 b/min. Cases with extreme tachycardia over 140 b/min are

TABLE 1. Physiological data on admission (see text for abbreviations)

	DIR	MED	P
BP (mmHg)	139.4 ± 40.7	139.5 ± 41.7	ns
PR (beasts/min)	94.2 ± 27.4	91.7 ± 26.6	ns
PCO_2 (mmHg)	41.6 ± 16.0	39.4 ± 11.0	<0.05
PO_2 (mmHg)	161.2 ± 131.7	204.6 ± 153.3	<0.01

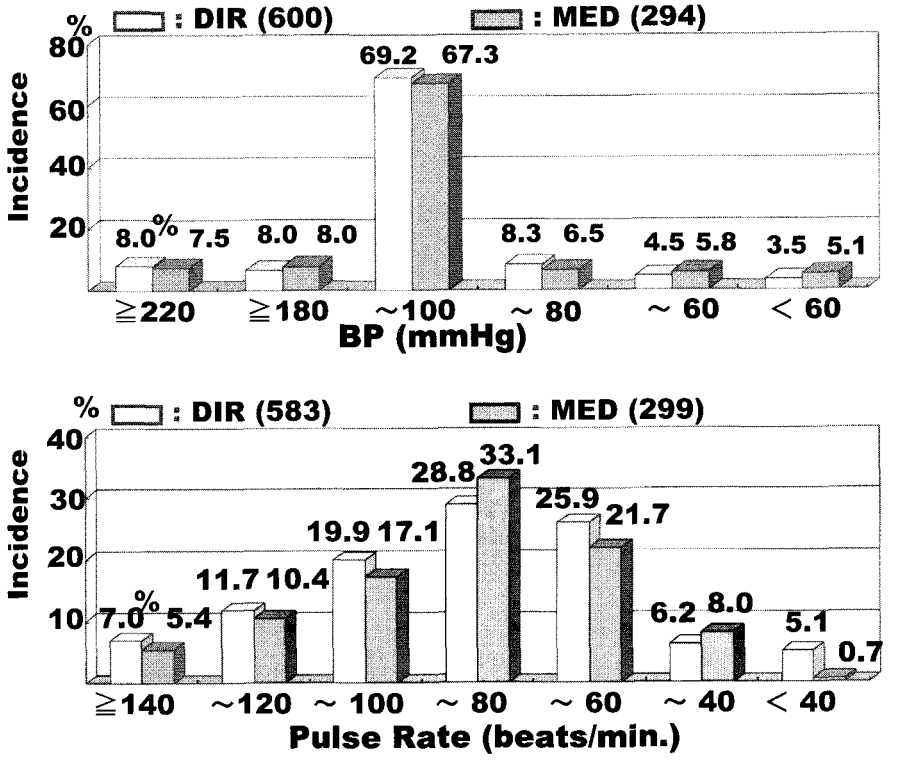


FIG. 1. Distribution of BP and PR on admission in DIR and MED group. Distribution pattern is almost same in both groups, while some subtle differences are present. Details are described in the text

observed in 7.0% of DIR and in 5.4% of MED, of which difference is not significant. Conversely, cases with extreme bradycardia less than 40 b/min are present in 5.1% of DIR, while only in 0.7% (two cases) of MED goroup (Fig. 1, bottom).

A distribution of PCO_2 on admission shows that only 43.1% of DIR and 48.3% of MED are in physiological range of 35 to 45 mmHg. Detrimental hypercapnia with PCO_2 above 55 mmHg is observed in 10.4% of DIR and in 6.9% of MED, while excess hypocapnia with PCO_2 below 25 mmHg is present in 5.3% of DIR and 3.0% of MED.

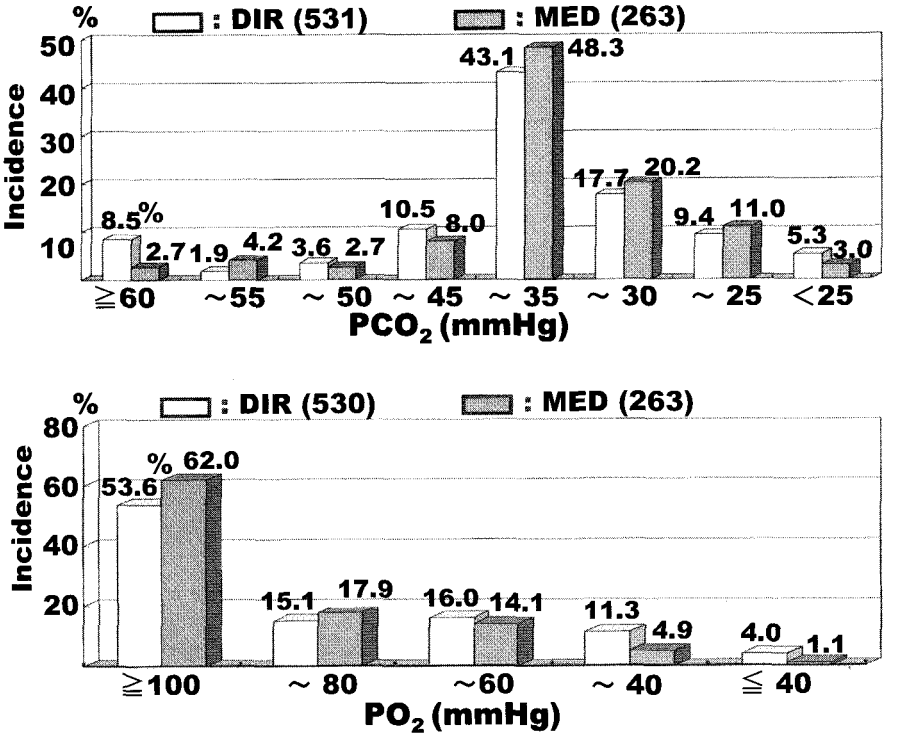


FIG. 2. Distribution of PCO_2 and PO_2 level on admission in DIR and MED group. Some significant difference in extraordinary ranges are noticeable, though distribution pattern is essentially similar in both groups. See the text for details

Approximately 80% of patients are existing in permissible range with some in detrimental hypercapnic levels (Fig. 2, top). Hypercapnia with PCO_2 level above 55 mmHg is seen in 10.4% of DIR and 6.9% of MED, which is significantly different. However, restricting PCO_2 level within from 55 to 60 mmHg, significantly more cases are present in MED than in DIR (4.2% *vs* 1.9%) (Fig. 3, top).

PO_2 distribution in both groups shows that 53.6% of DIR and 62.0% of MED are with PO_2 above 100 mmHg, and 15.3% of the former and 6.0% of the latter are severely hypoxic with PO_2 below 60 mmHg (Fig. 2, bottom). Incidence of cases showing hypoxia with PO_2 level 60 mmHg or less is 15.3% in DIR and 6.0% in MED, that is significantly different (Fig. 3, bottom).

Among 151 cases depicted as coma on admission in MED group, only 33 cases (21.9%) underwent endotracheal intubation (ETI) at previous hospitals. However, physiological data of those with and without ETI at previous hospitals are not different, except as to oxygenation, which is significantly better in the former group (Table 2). Glasgow Outcome Scale scores at discharge in these two groups are not different. Mortality is almost 60% in both groups (Fig. 4).

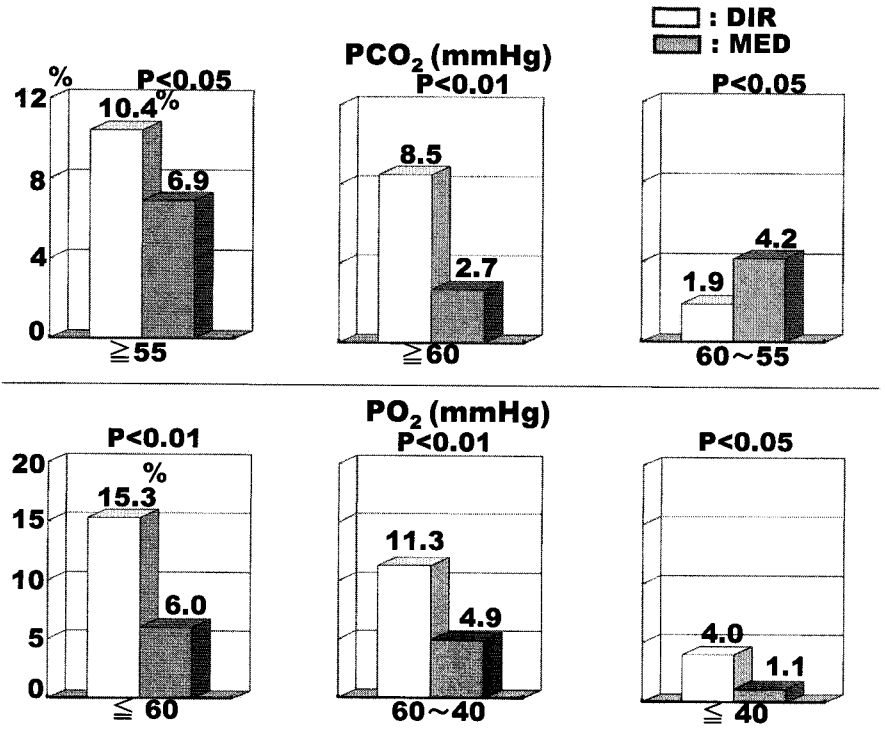


FIG. 3. Differences of blood gas data of DIR and MED group. Top: incidence of hypercapnic case is higher in DIR than in MED except for those with PCO_2 level between 55 to 60 mmHg. Bottom: incidence of hypoxic case is definitely higher in DIR than in MED, while extremely hypoxic cases are present even in MED group. See the text for further details

TABLE 2. Physiological data of MED group on admission

	Intubated	Non-intubated	*P*
BP (mmHg)	128.1 ± 48.9	134.6 ± 45.5	ns
PR (beasts/min)	98.3 ± 27.7	93.4 ± 28.2	ns
PCO_2 (mmHg)	42.5 ± 11.6	40.6 ± 12.1	ns
PO_2 (mmHg)	274.8 ± 162.6	209.5 ± 154.1	<0.05

4 Discussion

Importance of early medical intervention and resuscitation to prevent hypotension and/or hypoxia for severely injured traumatic patients is well recognized by medical care providers working at every field of emergency medicine [1-4]. As cited in the guidelines for TBI of the U.S.A. [5,6] and of Japan [1], these procedures are particularly important in treatment for patients with severe TBI. Despite of recommendations of these guidelines, numbers of reports revealed that prehospital medical care

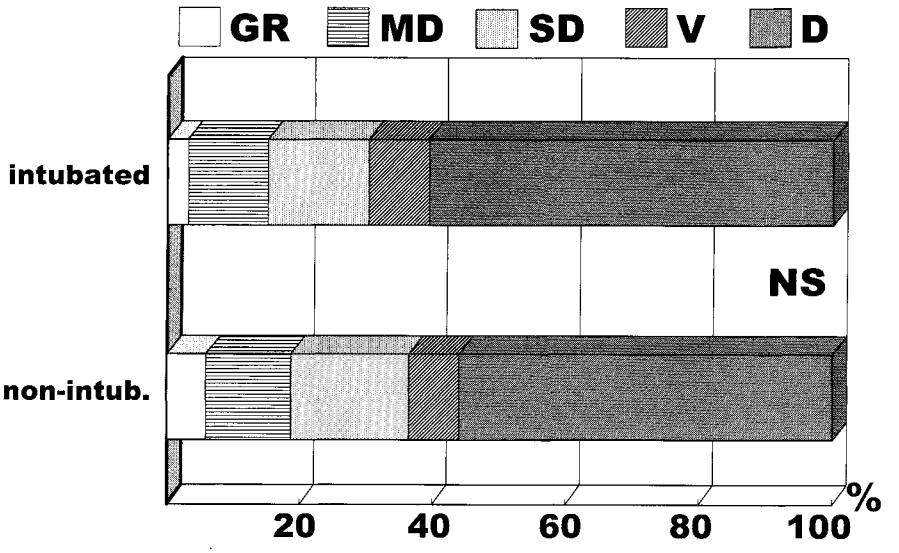


FIG. 4. Glasgow Outcome Scale score at discharge of cases with of without ETI. Outcome at discharge is quite the same in cases with or without ETI

especially as to maintaining blood pressure and/or oxygenation for patients with TBI is not always satisfactorily performed [8–10]. In Japan, PTHp medical care is given essentially by physicians of primary or secondary emergency hospitals or by an ambulance rescue team comprising paramedics and assistant rescue crews, who can provide medical practices which are strictly limited by laws to a patient at accident scenes. In consequence, there must be a distinct difference between physiological data obtained immediately after admission to tertiary emergency institutions from patients of DIR group and from those of MED one.

Nevertheless, there was no difference as to an average admission BP in DIR and MED groups, and BP was kept in acceptable range (80–180 mmHg) in approximately 75% of cases in both groups. However, 8.0% of DIR and 10.9% of MED showed hypotension lower than 80 mmHg, and 3.5% and 5.1% of respective group were in dangerous shock state below 60 mmHg. Besides, 8 percent and 7.5% of those groups were at dangerously hyperternsive state above 220 mmHg (Fig. 1, top). Concerning to an average PR, there was no difference between the two groups, of which 74.6% in DIR and 71.9% in MED were at acceptable level from 60 to 120 b/min (Fig. 1, bottom). Distribution pattern of BP and PR are quite the same in the two groups, and incidence of cases exhibiting these two indicators (BP or PR) at abnormal level is not different between these two groups (Fig. 1, top and bottom). These findings suggest that PTHp medical care might have been insufficient or inappropriate especially in cases with poorer vital signs. An extreme hypoxia or tachy- or bradycardia must be corrected by physicians at praimary or sencondary institutues to make incidence of these abnormality be significantly lower in MED group than in DIR one.

As to data relating to respiratory conditions during transportation or on admission to tertiary institutions, numbers of differences were observed between DIR and MED

groups. Regarding PCO_2 level, only 43.1% of DIR and 48.3% of MED group show normocapnia from 35 to 45 mmHg [9]. Undesirable hypercapnia with PCO_2 above 55 mmHg was observed in 10.4% of the former and 6.9% of the latter, while excess hypocapnia with PCO_2 lower than 25 mmHg, which might cause cerebral ischemia, was identified in 5.3% of DIR and 3.0% of MED [9] (Fig. 2, top). Despite of recommendations by the guidelines for TBI [1,5,6], recent reports disclosed considerable portion of cases with TBI shows hypocapia [9,10]. Excess hypocapnia of limited time could be acceptable confining to PTHp medical care [10], but hypercapnia, which potentially causes intracranial hypertension, should be avoided by applying pertinent assisted ventilation with or without ETI. In this regard, the present data shows that MED group was treated better comparing to DIR one, because incidence of hypercapnic case is significantly lower in MED than in DIR group (Fig. 3, top). However, restricting the cases with PCO_2 level within from 55 to 60 mmHg, significantly more cases were in MED than in DIR, of which incidence was 4.2% and 1.9% respectively (Fig. 3, top-right column). This inverse figure strongly suggests that medical care at PTHp institutions was insufficient at least concerning ventilatory support for cases with hypercapnia at this level.

An average PO_2 level on admission was significantly higher in MED group than in DIR one. This relationship is unchanged at any level of hypoxic state (Fig. 3, bottom). Because arterial PO_2 level is stable for much longer period of time than PCO_2 level, this result obtained from the data on admission definitely reveals that physicians in PTHp institutions paid sufficient attention to provide oxygen supply to a patient with TBI. Yet, the fact that 6.0% of MED group show PO_2 level below 60 mmHg, which is definitely hazardous level at acute phase of trauma care, must be considered as a serious problem.

As paramedics are not allowed to provide ETI to a trauma patient unless he shows cardio-pulmonary arrest in Japan, data concerning ETI can be studied only in cases of MED group. Only 21.9% of definitely comatose patients underwent ETI at PTHp institution. This might be able to partly explain why considerable numbers of cases in MED exhibited hypercapnic state on admission. It is regretful that there are physicians in primary or secondary emergency hospitals who are unwilling or not experienced well to practice ETI at emergency situation. Efficacy of ETI for severely injured patient at accident scene is still on controversy [2,7–10], but it must be true that, in case of a patient being in a emergency medical institution, physicians should not hesitate to give ETI to him if he is in coma. This is discouraging data, and we should institute more active, effective and nation-wide extensive pre-hospital medical care education program for medical staff in order to improve emergency medical care for acute traumatic case at primary or secondary institutions. Fortunately, physiological data on admission are not different in cases with or without ETI, except for that better oxygenation is maintained in the former group (Table 2). Outcome of these two groups is also not different so far as judging from Glasgow Outcome Scale score at discharge from tertiary emergency institution (Fig. 4). However, further follow-up for longer period of time including tests for higher brain functions must be necessary to know precisely if there are some subtle differences between these two groups or not. In Japan, now we are advancing the system of on-site intubation by specially trained rescue paramedics, and these data might ask reconsideration for the efficacy of rapid introduction of such medical technique in emergency situation.

5 Conclusion

Physiological data of 1002 cases of JNTDB were analyzed to compare differences between DIR and MED group. BP and PR are essentially same in both groups although there are considerable numbers of cases who show detrimental abnormality as to these parameters. On the other hand, regarding parameters representing respiratory condition, significantly more hypercapnic or hypoxic cases are present in DIR group, while some seriously hypercapnic or hypoxic ones do exist in MED group. Another serious problem is that only one fifth of comatose cases in MED received ETI at PTHp institutions, although physiological data and outcome at discharge are not different in groups with or without ETI.

References

1. Tokutomi T (2003) Traumatic brain injury. *Emerg Medicine (Tokyo)* 27:1741–1746
2. Yanagawa Y, Takasu A, Saitou T, et al (2004) Analysis of prehospital care provided by doctor car in our institute for patients with head trauma. *J Japan Association for Acute Medicine* 15:175–179
3. Cooper DJ, Myles PS, McDermott FT, et al (2004) Prehospital hypertonic saline resuscitation of patients with hypotension and severe traumatic brain injury. *JAMA* 291:1350–1357
4. Rudehill A, Bellander B, Weitzberg E, et al (2002) Outcome of traumatic brain injuries in 1508 patients: Impact of prehospital care. *J Neurotrauma* 19:855–868
5. Adelson PD, Bratton SL, Carney NA, et al (2003) Resuscitation of blood pressure and oxygenation and prehospital brain-specific therapies for the severe pediatric traumatic brain injury patient. *Pediatr Crit Care Med* 4 (Suppl.):S12–S18
6. Gabriel EJ, Ghajar J, Jagoda A, et al (2002) Guidelines for prehospital management of traumatic brain injury. *J Neurotruama* 19:111–174
7. Bulger EM, Copass MK, Sabath DR, et al (2005) The use of neuromuscular blocking agents to facilitate prehospital intubation does not impair outcome after traumatic brain injury. *J Trauma* 58:71–724
8. Davis DP, Peay J, Sise J, et al (2005) The impact of prehospital endotracheal intubation on outcome in moderate to severe traumatic brain injury. *J Trauma* 58:933–939
9. di Bartolomeo S, Sanson G, Nardi G, et al (2003) Inadequate ventilation of patients with severe brain injury: A possible drawback to prehospital advanced trauma care? *Eur J Emerg Med* 10:268–271
10. Thomas SH, Orf J, Wedel SK, et al (2002) Hyperventilation in traumatic brain injury patients: Inconsistency between consensus guidelines and clinical practice. *J Trauma* 52:47–53

Key Word Index