JOINT MEETING

American Academy of Neurological Surgery

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German Academy of Neurosurgery

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German Society of Neurosurgery

TASCHENBERGPALAIS DRESDEN, OCTOBER 5-8, 2004

TABLE OF CONTENT

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2004 Joint Meeting of the
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and the
German Society of Neurosurgery

REGISTRATION DESK LOCATION AND HOURS:

October 5-8, 2004, Dresden
Kempinski Hotel Taschenbergpalais
Lobby

Tuesday, October 5	10:00 am – 7:00 pm
Wednesday, October 6	7:30 am – 6:00 pm
Thursday, October 7	7:30 am – 6:00 pm

HOTEL INFORMATION

October 5-8, 2004

Kempinski Hotel Taschenbergpalais
Taschenberg 3
D-01067 Dresden
Germany

Phone: 011-49-351 49 12 0
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PROGRAM SUMMARY

TUESDAY, OCTOBER 5

EVENT	TIME	LOCATION
Bus transportation to Dresden	10:30 am	Departing from Four Seasons Lobby
Arrival at Kempinski Taschenbergpalais	1:30 pm	Hotel
Registration Lobby	10:00 am – 7:00 pm	Taschenbergpalais
Scientific Session	2:30 pm – 6:45 pm	Kurfürstensaal A
Opening Reception	7:15 pm – 10:15 pm	Bel Etage

PROGRAM FOR SPOUSES

Afternoon Tea	2:30 pm	Bel Etage

PROGRAM SUMMARY

WEDNESDAY, OCTOBER 6

EVENT	TIME	LOCATION
Registration	7:30 am – 6:00 pm	Hotel Lobby
Business Breakfast	7:30 am – 8:30 am	Kurfürstensaal B
Meeting **For American Academy Members Only**		
Business Breakfast Meeting **For German Academy Members Only**	7:30 am – 8:30 am	Bel Etage
Guest/Spouse Breakfast	7:30 am – 10:30 am	Bel Etage
Scientific Session	8:30 am – 12:30 pm	Kurfürstensaal A
Snack Buffet	5:00 pm – 6:30 pm	Bel Etage

PROGRAM FOR SPOUSES

Guided bus tour to Meissen & Meissen Porcelain Factory	8:30 am - 1:00 pm	Departure from hotel lobby
Walking tour through the heart of Dresden	2:00 pm – 4:00 pm	Departure from hotel lobby
Golf	1:30 pm	Elbflorence course
Tennis	1:30 pm	Tennis Club "Blau Weiß Dresden e.V."

OFFSITE EVENT

Semper Opera Performance of Beethoven's "Fidelio"	7:00 pm – 9:45 pm	within walking distance (2-5 minutes)

PROGRAM SUMMARY

THURSDAY, OCTOBER 7

EVENT	TIME	LOCATION
Registration	7:30 am – 6:00 pm	Hotel Lobby
Business Breakfast Meeting **For American Academy Members Only**	7:30 am – 8:30 am	Kurfürstensaal B
Business Breakfast Meeting **For German Academy Members Only**	7:30 am – 8:30 am	Bel Etage
Guest/Spouse Breakfast	7:30 am – 10:30 am	Bel Etage
Scientific Session	8:30 am – 1:00 pm	Kurfürstensaal A
PROGRAM FOR SPOUSES		
Guided tour of Old Masters Gallery of Arts Or Guided tour of Museum of the Green Vault Treasury	9:45 am – 11:30 am 10:00 am – 11:30 am	Departure from hotel lobby
Presidential Address	12:15 pm – 1:00 pm	Kurfürstensaal A/B
Bus tour to the baroque hunting lodge, "Schloss Moritzburg"	2:00 pm – 5:00 pm	Departure from hotel lobby
Golf	1:30 pm	Elbflorence course
Tennis	1:30 pm	Tennis Club "Blau Weiß Dresden e.V."
DINNER		
Cocktail Reception	7:00 pm – 7:30 pm	Residence Castle
Black Tie Dinner and Dance	7:30 pm	Residence Castle (within walking distance, 2-5 minutes)

FRIDAY, OCTOBER 8

EVENT	TIME	LOCATION
Breakfast for members, guests, and spouses	6:30 – 10:30 am (on your own)	Bel Etage

SOCIAL ACTIVITIES FOR SPOUSES

Tuesday, October 5

2:30 pm	Afternoon tea at the Bel Etage
7:15 pm – 10:15 pm	Opening reception at the Bel Etage

Wednesday, October 6

7:30 am – 10:30 am	Guest/spouse breakfast at the Bel Etage
8:30 am – 1:00 pm	*Guided bus tour to the 1000-year-old town of Meissen (includes a guided tour of the renowned Meissen Porcelain Factory). Departs from the hotel lobby.
1:30 pm	*Golf at Elbflorence Course or Tennis at Tennis Club "Blau Weiß Dresden e.V."
2:00 pm – 4:30 pm	*Guided walking tour through the historical heart of Dresden, including Royal Palace, the Zwinger, and the Cathedral. Departs from the hotel lobby.
5:00 pm – 6:30 pm	Snack buffet at the Bel Etage
7:00 pm – 9:45 pm	*Semper Opera Performance of Beethoven's "Fidelio"

Thursday, October 7

7:30 am – 10:30 am	Guest/spouse breakfast at the Bel Etage
9:45 am – 11:30 am	*Guided walking tour of the Old Masters Gallery of
or	Arts
10:00 am – 11:30 am	*Guided walking tour of the Museum of the Green Vault Treasury. Departs from the hotel lobby.
12:15 pm – 1:00 pm	Presidential Address Kurfürstensaal A/B
1:30 pm	*Golf at Elbflorence Course or Tennis at Tennis Club "Blau Weiß Dresden e.V."
2:00 pm – 5:00 pm	*Guided bus tour to the baroque hunting lodge, "Schloss Moritzburg", 18th century residence of King August the Strong during hunting season. Departs from the hotel lobby.
7:00 pm – 7:30 pm	Cocktail reception at the Residence Castle (within walking distance)
7:30 pm	Black Tie Dinner and Dance at the Residence Castle

Friday, October 8

(on your own)	Breakfast for all members, guests, spouses at the Bel Etage

* Activities require prior registration.

SCIENTIFIC PROGRAM
Joint Meeting of the American Academy of Neurological Surgery, the German Academy of Neurosurgery and the German Society of Neurosurgery, Dresden, Germany
October 5–8, 2004

TUESDAY, OCTOBER 5	DRESDEN
2:30–2:45 pm	Reflections on Joint Meetings between the American Academy of Neurological Surgery and German Neurosurgeons. Rudolf Fahlbusch
2:45–4:30 pm	**Scientific Paper Presentations,** Moderators: James Rutka, Hans-Peter Richter
2:45-3:00 pm	Cortical and Striatal Migration of Endogenous Adult Stem Cells from the Sub-ventricular Zone and Posterior Peri-ventricular Region in Response to Stroke. Robert J Dempsey, KA Sailor
3:00-3:15 pm	Genetic Variants of Matrix Metalloproteinase Genes and their Inhibitors in Patients with Intracranial Aneurysms. Dietmar Krex, IR König, A Ziegler, HK Schackert, G Schackert
3:15-3:30 pm	Downregulation of Potassium Channels after Subarachnoid Hemorrhage: a Possible Mechanism for Cerebral Vasospasm. BS Jahromi, Y Aihara, GW Weyer, E Nikitina, M Agbaje-Williams, D Ryan, R Yassari, Robert Loch Macdonald
3:30-3:45 pm	Prospective Evaluation of Surgical Microscope Based Indocyanine Green Video Angiography in Aneurysm Surgery. Andreas Raabe, P Nakaji, J Beck, J Kamerman, V Seifert, RF Spetzler

TUESDAY, OCTOBER 5 (continued)

3:45-4:00 pm	Multivariate Analysis of a Consecutive Prospective Series of Carotid Endarterectomies. Robert E Harbaugh, A Agarwal, V Chinchilli
4:00-4:15 pm	A Phase IIa, Multicenter, Double-blind, Placebo-controlled, Randomized Study to Assess the Safety and Tolerability of the Selective Endothelin A (ETA) Receptor Antagonist Clazosentan (AVX-034343) for the Prevention of Cerebral Vasospasm, Following Severe Aneurysmal Subarachnoid Hemorrhage (aSAH). Bernhard Meyer for the Axovan Study Group
4:15-4:30 pm	Endovascular Management of Intracranial Aneurysms: An Experience of 1321 Aneurysms in 1101 Patients: Single Center Experience. Robert H Rosenwasser, E Veznedaroglu, S Whang
4:30–4:45 pm	*Beverage Break*
4:45–6:45 pm	**Scientific Paper Presentations,** Moderators: Gabriele Schackert, Steve Papadopoulos
4:45-5:00 pm	Susceptibility of Murine Neural Stem Cells and Tumor Cells to Respond to Regenerative Signals of Axolotl Tissue. Matthias Kirsch, E Schnapp, E Tanaka, G Schackert, HK Schackert
5:00-5:15 pm	Local Delivery of a Fragment of Human Endostatin Combined with Systemic Administration of BCNU Prolongs Survival in a Rodent Experimental Glioma Model. Alessandro Olivi, FG Legnani, G Pradilla, BM Tyler, F Chillemi, F DiMeco

TUESDAY, OCTOBER 5 (continued)

5:15-5:30 pm	Expression of Hypoxia-inducible Carbonic Anhydrases in Brain Tumors. Martin Proescholdt, C Mayer, M Merril, A Brawanski
5:30-5:45 pm	Anti-EGFR Monoclonal Antibody Cetuximab Augments Radiation and Chemotherapeutic Effects in Glioblastoma Multiforme *in vitro* and *in vivo*. JL Eller, SL Longo, MM Kyle, D Bassano, DJ Hicklin, Gregory W Canute
5:45-6:00 pm	Multicentric Phase III Study, Fluorescence-guided Resection of Malignant Gliomas with 5-ALA: Preliminary Results on Interim Analysis of 270 Assessable Patients. Walter Stummer, T Meinel, the ALA-Glioma Study Group, U Pichlmeier, OD Wiestler, FE Zanella, HJ Reulen
6:00-6:15 pm	Is Gross Total Resection Sufficient Treatment for Posterior Fossa Ependymomas? L Rogers, J Pueschel, Robert Spetzler, W Shapiro, S Coons, T Thomas, B Speiser
6:15-6:30 pm	Management of Optic Nerve Sheath Meningiomas. U Schick, Werner Hassler
6:30-6:45 pm	The Role of Endogenous Growth Hormone-Releasing Hormone (GHRH) in Acromegaly. William F Chandler, EV Dimaraki, AL Barkan, MB Brown, V Padmanabhan, SY Kim, R Taussig

WEDNESDAY, OCTOBER 6 DRESDEN

8:30–9:15 am	**Point - Counterpoint Debate** Intraoperative MRI, Gimmick or Godsend? Robert Spetzler and Rudolf Fahlbusch
9:15-10:30 am	**Scientific Paper Presentations** Moderators: William Couldwell, Johannes Schramm
9:15-9:30 am	Selection of the Optimal Entry Zone to the Brain Stem for Removal of Intraaxial Cavernous Angiomas. Helmut Bertalanffy
9:30-9:45 am	Transgenic Arteriovenous Fistula in the Rat: an Experimental Model of Gene Therapy for Brain Arteriovenous Malformations. Michael T Lawton, CL Stewart, AA Wulfstat, N Derugin, T Hashimoto, WL Young
9:45-10:00 am	Role of EphB4 Signaling in the Regulation of Vascular Morphogenesis and Vascular Permeability in Malignant Glioma. Peter Vajkoczy, R Erber, U Eichelsbacher, V Powajbo, P Knyazev, A Ullrich
10:00-10:15 am	Gamma Knife Radiosurgery in the Management of Glomus Tumors—A Volumetric Study of 17 cases. Gene H Barnett, A Varma, JH Suh, J Ross
10:15-10:30 am	Intraoperative Functional MRI. First Results and Technical Considerations. Thomas Gasser, D Stolke, R Fahlbusch, C Nimsky
10:30–10:45 am	*Beverage Break*
10:45–12:30 pm	**Scientific Paper Presentations** Moderators: James Rutka, Dietmar Stolke
10:45-11:00 am	Sirolimus-Eluting Stents in the Canine Cerebral Vasculature: Assessment of Safety Profile and Vessel Response. Elad I Levy, RA Hanel, AS Boulos, FO Tio, AM Paciorek, KS Kagan-Hallet, MD Fronckowiak, LR Guterman, LN Hopkins

WEDNESDAY, OCTOBER 6 (continued)

11:00-11:15 am	Brain Tumor Surgery in the Vicinity of Short-Term Memory Representation—Results of Neuronavigation using fMRI Images. Veit Braun, A Albrecht, A Wunderlich, H-P Richter
11:15-11:30 am	Fiber Tract Deformation as Visualized with Sequential Acquisitions of 3D-Ultra-Sound (3DUS) During Intracranial Surgery. Volker A Coenen, T Krings, J Weidemann, FJ Hans, P Reinacher, JM Gilsbach, V Rohde
11:30-11:45 am	**German Society First Prize Award - (Wilhelm Tönnis Preisträger)** Mechanical Response of a Cervical Spine Motion Segment on Removing a Local Autograft. Tobias Pitzen, CJ Kempf, TR Oxland, WI Steudel,
11:45-12:00 noon	**American Academy Honorable Mention Award** Selective Ablation of Vanilloid Receptor 1 Positive Nociceptive Neurons for Elimination of Hyperalgesia and Neuropathic Pain. Russell R Lonser, GC Tender, S Walbridge, Z Olah, L Karai, M Iadarola, EH Oldfield
12:00-12:15 pm	**German Academy First Prize Award** Identification of Brain Tissue Necrosis by MRI: Validation by Histomorphometry. Michael Stoffel, C Blau, H Reinl, J Breidt, K Gersonde, A Baethmann, N Plesnila
12:15-12:30 pm	**American Academy First Prize Award** Achieving a Multidimensional Brain Computer Interface in Humans Using Electrocorticographic Signal. Eric Leuthardt, G Schalk, JR Wolpaw, JG Ojemann, DW Moran

THURSDAY, OCTOBER 7	DRESDEN
8:30-9:15 am	**Point - Counterpoint** The Fate of the Academic Neurosurgeon, Viewpoints from the United States: Peter Black, and Germany: Hans-Peter Richter
9:15-10:45 am	**Scientific Paper Presentations** Moderators: Steve Papadopoulos, Hansdetlef Wassman
9:15-9:30 am	Clinical Outcome Following Transforaminal Lumbar Interbody Fusion (TLIF): One Year Follow-up of Prospective Data. Richard G Fessler
9:30-9:45 am	Application of Image-Guided Spinal Navigation to Decompression and Internal Fixation of the Upper Cervical Spine. Iain H Kalfas
9:45-10:00 am	Laboratory Testing of an Implantable Microsensor System for Intraoperative 3D-Computer Animation of Vertebral Body Motion in Cervical Spinal Surgery. Olaf Süss, T Kombos, S Schönherr, S Mularski, B Kühn, M Brock
10:00-10:15 am	Transthoracic Discectomy without Interbody Fusion. D Edwards, A Cohen-Gadol, William E Krauss
10:15-10:30 am	Treatment of Spinal Cord Injury via Topical Perfusion with an ATP Solution. Christopher B Shields, YP Zhang, S Chien, Y Han, LBE Shields, M Li, B Chiang, DA Burke
10:30-11:00 am	*Beverage Break*

THURSDAY, OCTOBER 7 (continued)

11:00 am -1:00 pm	**Scientific Paper Presentations** Moderators: Joachim Gilsbach, James Rutka
11:00-11:15 am	"IOMaster 7D" - a New Device for Virtual Neuroendoscopy. Christos Trantakis, J Meixensberger, G Strauβ, E Nowatius,D Lindner, HK Cakmak, H Maaβ, C Nagel, U Kühnapfel
11:15-11:30 am	Fedor Krause, The Krause Operations, and Krause's Impact on American Neurosurgeons. Peter W Carmel, M Buchfelder
11:30-11:45 am	Diffusion Tensor Imaging for 3-D Fiber Tract Visualization in Navigated Glioma Surgery. Christopher Nimsky, O Ganslandt, AG Sorensen, R Fahlbusch
11:45-12:00 noon	Changes of the Astrocytic Matrix and Reappearance of Radial Glia in Hippocampi of Patients Suffering From Temporal Lobe Epilepsy. Thomas M Freiman, J Eismann, M Frotscher, J Zentner
12:00-12:15 pm	Surgical Treatment of Hemispheric Intractable Epilepsy in Childhood With Functional Hemispherectomy or Peri-Insular Hemispherectomy. Falk Oppel, V Zountsas, HW Pannek
12:15-1:00 pm	**Presidential Address:** Volker Sonntag, *to be introduced by Bill Chandler*
1:00 pm	**Concluding Remarks:** Rudolf Fahlbusch, Volker Sonntag, Dietmar Stolke

Meeting Adjournment

TUESDAY, OCTOBER 5 **2:45-3:00 pm**

Cortical and Striatal Migration of Endogenous Adult Stem Cells from the Sub-Ventricular Zone and Posterior Peri-ventricular Region in Response to Stroke.

Robert Dempsey, KA Sailor

University of Wisconsin

The proliferation of endogenous adult stem cells represents a potential therapy for repair after a stroke. Adult neurogenesis is a phenomenon that occurs in the subventricular zone (SVZ) at the lining of the lateral ventricles and in the dentate gyrus (DG) of the hippocampus, and has been shown to be stimulated by various interventions including stroke. Migration of these cells is necessary for them to repopulate a region of stroke damage. Normally the adult stem cells located in the SVZ are only seen migrating anteriorly to the olfactory bulbs where they differentiate into olfactory interneurons. After 1 hour of focal cerebral ischemia in rats, and at 2, 4, 6 and 8 days of reperfusion, we observed these cells also migrating laterally, extending their axons in their path of migration toward the infarct, into the striatum. These cells were labeled with the immature migrating neuronal marker doublecortin (DCX) and the extent of the migration was correlated with the amount of injury to the striatum. In addition to this, we have observed cells in the posterior peri-ventricular region (pPV), a posterior extension of the SVZ, migrating directly to the ipsilateral cortex. By imaging these regions at two-day time intervals we were able to observe an abrupt increase in proliferation in the ipsilateral pPV at day 2 after ischemia, with localized migration along the corpus callosum. By days 8 and 12, we observed DCX positive cells that had migrated laterally into the ischemic penumbra with their axons extending into the ischemic core. This study demonstrates that there is an endogenous response to injury by these cells. By understanding the factors that attract such cells, future therapies may enhance this migration for possible restoration of function to the damaged region of the brain.

Genetic variants of matrix metalloproteinase genes and their inhibitors in patients with intracranial aneurysms

Dietmar Krex[1], IR König[3], A Ziegler[3], HK Schackert[2], G Schackert[1]

[1]Department of Neurosurgery and [2]Department of Surgical Research, University Hospital Carl Gustav Carus, University of Technology, Dresden, and [3]Institute of Medical Biometry and Statistics (I.R.K., A.Z.), University at Lübeck, Germany

Objective: There are several lines of evidence that remodelling of the extracellular matrix is a crucial event in the pathogenesis of cerebral aneurysms. Matrix-metalloproteinases (MMPs) are the most important degrading enzymes in the extracellular matrix. Their activity is predominantly controlled by tissue inhibitors of metalloproteinases (TIMPs). To investigate the possible impact of genetic variants within the genes encoding *TIMP-1*, *-2*, and *-3*, and *MMP-2*, *-3*, *-9*, and *-14*, respectively, we conducted a case-control study.

Methods: The entire coding regions and parts of the promoter sequences of the referring genes were investigated using the automated laser fluorescence (A.L.F.) technique. Genotypes and allele frequencies were determined in a primary study sample comprising 44 well defined aneurysm patients and 40 controls. Those being in Hardy-Weinberg disequilibrium were analyzed in another sample of 40 cases and 40 controls, respectively. Odds ratios (ORs) and exact 95% confidence intervals (CIs) were calculated to compare allele frequencies and genotype frequencies using the Cochrane-Armitage trend test.

Results: A total of 38 single nucleotide polymorphism (SNPs) were identified; 3, 4, and 2 in *TIMP-1*, *-2*, and *-3* genes, and 10, 4, 11, and 4 in *MMP-2*, *-3*, *-9*, and *-14* genes, respectively. SNPs -621C>T, -596A>C, -261G>A of the *TIMP-2* gene were new identified polymorphisms. Deviations from Hardy-Weinberg equilibrium were particularly found for *MMP-2* and *MMP-9* SNPs, however, there were no significant differences in genotype and allele frequencies in those or between any of the other groups.

Conclusions: Our analysis of the entire coding region of three *TIMPs* and four *MMPs*, which are main contributors to extracellular matrix remodelling in vessel walls, failed to show an association of genetic polymorphisms with an intracranial aneurysm. However, deviations from Hardy Weinberg equilibrium found for *MMP-2*, and *MMP-9*, but also for *MMP-3*, and *TIMP-1* SNPs suggest that there might be additional more distantly located genetic variants of functional impact, which are the subject of ongoing studies.

Downregulation Of Potassium Channels After Subarachnoid Hemorrhage: A Possible Mechanism For Cerebral Vasospasm

Robert Loch Macdonald, BS Jahromi, Y Aihara, G Weyer, E Nikitina, M Agbaje-Williams,

Cerebral vasospasm remains a significant adverse prognostic factor for outcome after subarachnoid hemorrhage (SAH) and is a significant cause of morbidity and mortality in such patients. The pathogenesis remains ill-defined but it is clear that the narrowing is primarily due to abnormally sustained contraction of arterial smooth muscle cells. Cerebrovascular arterial constriction is regulated by membrane potential which in turn is determined by potassium conductance.
These studies examined expression of the major potassium channels by real time polymerase chain reaction and Western blotting and their function using whole cell and perforated patch clamp electrophysiology in normal dog basilar artery smooth muscle cells and in these cells obtained during vasospasm 7 days after SAH.
There were no significant changes in messenger ribonucleic acid and protein of the large-conductance, calcium-activated potassium channel (BK, alpha and beta subunits). There was significant downregulation of Kv2 class of voltage-gated potassium channels. Furthermore, of the two dominant potassium conductances in cerebrovascular smooth muscle cells, BK currents were unaffected by SAH whilst Kv2 class currents were nearly halved after SAH. Immunohistochemistry confirmed localization of Kv 2 (Kv2.1, 2.2) class channels to normal dog basilar smooth muscle and showed that immunoreactivity was reduced after SAH. Vasospastic myocytes were depolarized and showed decreased contribution of potassium conductance towards maintenance of membrane potential. Pharmacological block of Kv but not BK channels in control myocytes mimicked the depolarization observed in vasospastic myocytes and contracted basilar artery rings.
We propose that decreased Kv channel function contributes to the pathogenesis of cerebral vasospasm after SAH.

Prospective evaluation of surgical microscope based indocyanine green video angiography in aneurysm surgery

Andreas Raabe, P Nakaji, J Beck, J Kamerman, V Seifert, RF Spetzler[1]

Department of Neurosurgery, Neurocenter, Johann Wolfgang Goethe University Frankfurt am Main, Frankfurt am Main, Germany and [1]Division of Neurological Surgery, Barrow Neurological Institute, St. Joseph's Hospital and Medical Center, Phoenix, Arizona

Objective: We report about the final results of a prospective trial comparing a new technique of surgical microscope based indocyanine green video angiography (ICGA) with intraoperative or postoperative DSA.

Method: ICGA was performed during aneurysm surgery using a newly developed setup with the Zeiss microscope (Zeiss, Oberkochen, Germany). A microscope integrated light source containing infrared excitation light illuminates the operating field. After intravenous injection of the indocyanine dye (25 mg), intravascular fluorescence of ICG from within vessels is imaged by a microscope video camera. Patency of parent, branching and perforating arteries and clip occlusion of the aneurysm as found by ICGA were compared to intraoperative or postoperative DSA findings. The study is expected to close in May after inclusion of 100 patients.

Results: After including 90% of cases, 153 ICGA procedures were performed. The results of ICGA were concordant with postoperative DSA in 36 of 38 cases. One case of mild stenosis and one case of a 4 mm residual aneurysm were missed by ICGA. Compared with intraoperative DSA, the results of ICGA were concordant in 36 of 41 cases. In 4 cases a mild stenosis and in one case a severe stenosis was missed by ICGA. All false negative ICG findings were inconsequential. ICGA led to clip intraoperative clip correction in 7% of cases. None of the cases had clip correction after intraoperative or postoperative DSA when performed after ICGA. The final results will be reported at the meeting.

Conclusions: Microscope based ICGA is simple and provides real-time information about the patency of arterial and venous vessels of all relevant diameters and about the aneurysm sac. ICGA may fill the gap between intraoperative DSA and intraoperative Doppler. It may be used as an alternative to intraoperative DSA in many cases.

Multivariate Analysis of a Consecutive Prospective Series of Carotid Endarterectomies

Robert E. Harbaugh, A Agarwal, V Chinchilli

Departments of Neurosurgery and Health Evaluation Sciences, Pennsylvania State University

Objective: We performed a multivariate analysis to determine predictors of adverse clinical outcomes following carotid endarterectomy (CEA). Numerous variables, including gender, age, medical comorbidities, contralateral internal carotid artery occlusion, choice of anesthetic, presentation and resident or faculty surgeon were evaluated in regard to the incidence of neurological and non-neurological perioperative complications.

Methods: A prospective series of nearly 1200 CEAs were analyzed. All patients were operated upon under the direction of one neurosurgeon (REH). Clinical outcomes measures evaluated were any stroke, death or myocardial infarction within 30 days of operation. All patients were followed to a clinical endpoint and/or six weeks postoperatively. All outcomes were adjudicated by third party observers.

Results: The ipsilateral stroke rate within 30 days of CEA was 2.25%. None of the commonly cited risk factors such as advanced age, medical co-morbidities or contralateral carotid occlusion were associated with a significantly ($P<0.05$) increased risk of perioperative morbidity or mortality. The use of regional anesthesia was associated with a significantly decreased risk of non-neurological perioperative complications. Other details of the multivariate analysis will be presented.

Conclusion: CEA using regional anesthesia can be performed in patients with advanced age, diabetes mellitus, atherosclerotic coronary vascular disease and contralateral ICA occlusion with acceptably low perioperative morbidity.
Key words: carotid endarterectomy, high risk patients, Multivariate analysis, outcomes analysis, perioperative complications, regional anesthesia

A phase IIa, multicenter, double-blind, placebo-controlled, Randomized study to assess the safety and tolerability of the selective endothelin A (ETA) receptor antagonist clazosentan (AXV-034343) for the prevention of cerebral vasospasm, following severe aneurysmal subarachnoid hemorrhage (aSAH)

Bernhard Meyer for the Axovan Study Group

Department of Neurosurgery, University of Bonn, Germany

Objective: To assess whether the endothelin A (ETA) receptor antagonist clazosentan can reduce the incidence and severity of angiographic vasospasm on Day 9 post rupture (primary endpoint) in a selected high-risk population of patients with aSAH (Fisher Grade ≥ 3 / Hunt&Hess Grade III to IV) compared to placebo.

Methods: The study was divided into a double-blind Part A (randomized continuous iv. Infusion of clazosentan 0.2 mg/kg/h versus placebo starting within 48h post aSAH up to Day 14 post rupture) and an open-label Part B (clazosentan 0.4 mg/kg/h for 12 h followed by 0.2 mg/kg/h up to Day 14 for patients with persistent vasospasm as documented by DSA on Day 9). The primary endpoint was determined in comparison to baseline-DSA via central evaluation, secondary variables included daily blood flow velocities by TCD, incidence of infarcts on CT and outcome according to NIH-SS/mGCS score on Day 14.

34 patients were recruited over a 7-month period in 5 centers (safety population: 16 clazosentan, 18 placebo, analyzed post-hoc according to ITT). 32 patients remained in the intent-to-treat A (ITT-A) and per protocol (PP) population (15 clazosentan, 17 placebo), 19 patients entered Part B and were analyzed according to ITT (ITT-B; 7 clazosentan, 12 post-placebo). Two-sided Fisher's exact test was used to compare the incidence of vasospasm. Differences in severity of vasospasm were tested with the Wilcoxon test.

Results: The ITT-A population showed a significant reduction in the occurrence and severity of angiographic vasospasm in the clazosentan group (p=0.008, relative risk reduction: 55%; from 88.2% to 40.0% and odds ratio of 0.089). Even after conservative analysis (i.e., counting deaths and cerebral vasospasms during Part B of the study as treatment failures in the ITT post-hoc population), there was still a trend towards a lower incidence (p=0.052) and severity (p=0.061) of vasospasm (relative risk reduction of 37%; from 88.9% to 56.3%).

A lower incidence of new infarcts was observed in patients randomized to clazosentan group (15.4% vs. 43.8%) and TCD measurements yielded lower median Lindegaard indices for patients randomized to clazosentan suggesting a milder form of vasospasm.

Conclusions: Clazosentan showed a statistically significant reduction in the frequency and severity of vasospasm compared with placebo. When subsequent analysis incorporating imputation rules for missing data was performed there was still a statistical trend in favor of patients treated with clazosentan. The incidence/severity of adverse events observed with clazosentan was comparable to placebo.

Endovascular Management of Intracranial Aneurysms: An Experience of 1321 Aneurysms in 1101 Patients: Single Center Experience

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Introduction/Purpose: Endovascular management of intracranial aneurysms has become an option in certain patient populations based on age, neurologic condition, and anatomical location.

Clinical Materials/Methods: At TJUH from July 1994 through December, 2003, 2294 patients were treated for intracranial aneurysms. Age range was 9 – 89 years. Out of this group, 1192 patients (52%) underwent transcranial surgery and 1101 patients (48%) underwent Endovascular treatment. Eight hundred and sixty-nine patients (78%) presented with SAH. Patient selection for endosacular occlusion was based on physiologic age, Neurologic grade, and anatomy. Patients were treated under general anesthesia with neurophysiologic monitoring and full heparinization.

Results: A technical failure rate of 16% was noted and 175 patients underwent transcranial surgery when the lesion could not be endovasculary treated. The rate of intraprocedural rupture was 1.4%. The rate of embolic events were 2.9% acutely (intraprocedural) and 5.9% delayed. Mortality related to the procedure was 2.5%. The complete occlusion rate was 64% in the first 5 years and was 205 in the last 4 years. To date 4.7% of patients have required retreatment due to recurrence and longer followup is demonstrating that this number is increasing. Thirty-six percent were G1,2 and had a good/fair outcome (GOS), 64% were G3, 4; 87% good/fair; 6% fair; 7% dead; G4; 28% fair, 52% poor, 20% dead. No patient was treated as a G5.

Conclusions: Endosacular occlusion of intracranial aneurysms is a reasonable alternate to microsurgical intervention, particularly in elderly patients and patients in poor neurological grade. Incomplete occlusion and durability remain problematic.

Susceptibility of murine neural stem cells and tumor cells to respond to regenerative signals of axolotl tissue.

Matthias Kirsch[1], E Schnapp[3], E Tanaka[3], G Schackert[1], HK Schackert[2]

[1]Neurosurgery, Carl Gustav Carus Universitätsklinikum, Department of Surgical Research[2], Technische Universität Dresden and
[3]Max-Planck-Institute for Cell Biologie and Genetics, Dresden

Objective: Regeneration of the nervous system in humans and other vertebrates is not sufficient to allow functional recovery. In contrast, urodele and axolotl amphibians are able to regrow organs, such as the limbs and the tail including the peripheral nerves and spinal cord representing central nervous system tissue. Several reports indicate that axolotl do not reject foreign tissue. In-vitro fusion of axolotl with murine cells were successful. The purpose of this study was to evaluate the ability of regenerative axolotl tissue to recruit transplanted vertebrate (mouse) cells to follow the regenerative process.

Methods: Cross-species xenotransplantation was evaluated, both the transplantation of murine neural progenitor cell precursors and of murine brain tumor cells into the regenerating tail of an axolotl and the transplantation of axolotl cell spheroids, spinal cord, or regenerating tail tissue into the chronic cranial window of nude mice.

Results: Temperature-adapted cells and tissues were transplanted. The regenerating axolotl blastema was invaded by murine neural progenitor cells which remained within the growth cone. Three days post.implantation, no living murine cells were observed. In the cranial window of mice, axolotl spinal cord and blastema pieces, as well as spheroids from cultured myotubes were implanted. None of the transplants showed invasion of single cells into the surrounding parenchyma. A steadily increasing number of cells were observed that underwent apoptotic cell death. On day four post-implantation, no viable axolotl cells remained in the murine environment. However, in vitro confrontation studies using spheroids and blastema tissue, revealed a shift of the vertebrate cells to a regenerative phenotype.

Conclusion: Xenotransplantation of axolotl cells into nude mice and murine pluripotent neural progenitor cells into the axoltol blastema did not induce a regenerating phenotype. In vitro experiments confronting tumor tissue and blastema revealed a phenotypic change revealing an increase of precursor markers. Similar responses were observed after transplantation of murine neural precursor cells into the normal and the regenerating axolotl tail.

Local delivery of a fragment of human endostatin combined with systemic administration of BCNU prolongs survival in a rodent experimental glioma model

Alessandro Olivi, FG Legnani, G Pradilla, BM Tyler, F Chillemi, and F Di Meco

Introduction: Endostatin is an anti-angiogenic agent currently tested for several solid malignancies. A fragment of endostatin (43 amino acids), easily synthesized with high stability and water solubility was incorporated into controlled-release polymers and tested to determine its efficacy when combined with conventional chemotherapy for treatment of experimental gliomas.

Methods: Cytotoxicity of the endostatin fragment against 9L gliosarcoma, and F98 glioma was determined in vitro. The fragment was incorporated into polyanhydride-poly-[bis-(carboxiphenoxy-propane)-sebacic-acid] (pCPP:SA) at different loading concentrations and its pharmacokinetics were analyzed in vitro. The rat cornea micropocket assay was used to evaluate the anti-angiogenic activity of the fragment/polymer formulations. Systemic toxicity and efficacy of locally delivered endostatin fragment/polymers combined with systemic BCNU were determined in Fischer 344 rats(n=64) using the intracranial 9L gliosarcoma model.

Results: Endostatin fragment showed significant cytotoxicity in vitro against 9L and F98. Comparable sustained release was seen by day 19 in all polymer formulations. Corneas implanted with 40% endostatin fragment/pCPP-SA polymers had a mean angiogenesis index of 4.5±0.7 when compared to 8.5±1.3 in controls ($p=0.01$). Survival was prolonged in animals treated with the combination of intracranial 40% endostatin fragment/pCPP:SA polymers and systemic BCNU (mean survival of 120 days) when compared to controls (mean survival 11 days, $p<0.001$, with 33% long term survivors).

Conclusions: Controlled release polymers can effectively deliver a biologically active fragment of endostatin in a sustained fashion. This novel endostatin fragment inhibits angiogenesis in vitro and in vivo, and exhibits a synergistic effect when combined with systemically delivered with BCNU in the intracranial 9L gliosarcoma model.

Expression of hypoxia - inducible carbonic anhydrases in brain tumors

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Objective: Malignant Gliomas are the most frequent intrinsic brain tumors in adults. Metabolically, these tumors display a distinct pattern: First, they show a high glucose utilization rate combined with significant levels of lactate production, probably due to aerobic glykolysis. Surprisingly, the intracellular pH of malignant brain tumors has been found to be significantly more alkaline compared to normal brain, whereas the extracellular space displays an acidic pH as demonstrated by *in vivo* studies using pH microelectrodes. Secondly, malignant gliomas display large areas of intratumoral hypoxia as shown *in vivo* by polarographic measurements as well as by PET studies using ^{18}F-misonidazole as hypoxia specific tracer. Carbonic anhydrase (CA) IX and XII are transmembrane isoenzymes which are induced by tissue hypoxia. They participate in the regulation of pH homeostasis by catalyzing the reversible hydration of carbon dioxide. We hypothesize, that CA IX and XII may be overexpressed in malignant brain tumors due to intratumoral hypoxia. Induction of these enzymes in brain tumors might contribute to an aggressive phenotype by improved acid clearance. The aim of our study was to investigate, whether brain tumors of different histology and grade of malignancy express elevated levels of CA IX and XII compared to normal brain.

Methods: We analyzed 112 fresh frozen tissue samples from primary and metastatic brain tumors for CA IX and XII expression by immunohistochemistry. 8 brain tissue samples obtained from patients who died from extracerebral disease were used as normal brain control. The staining was semiquantitatively graded by three independent investigators blinded to the underlying histology. To confirm the immunostaining results, Western Blot analysis was performed from total protein extract of the tumor tissue. The CA IX and XII mRNA expression was investigated by *in situ* hybridization. To correlate CA IX and XII with tissue hypoxia, immunohistochemical staining for hypoxia inducible factor (HIF-1) was performed on adjacent sections.

Results: While normal brain tissue showed minimal CA IX and XII expression, we found a profound upregulation of both enzymes in the brain tumor tissue both by immunohistochemistry and Western blot. The levels of CA IX and XII induction correlated with the grade of malignancy. CA IX and XII mRNA levels were elevated particularly around areas of micronecrosis. Accordingly, the highest levels of CA IX and XII protein expression was found to be in perinecrotic pseudopallisading cells indicating hypoxic induction. Also, comparison of CA IX and XII staining and HIF-1 staining revealed a similar microanatomical distribution, confirming hypoxia as the main factor of induction.

Conclusion: The results demonstrate that CA IX and XII are upregulated in intrinsic and metastatic brain tumors compared to normal brain tissue. Hypoxia seems to be the major mechanism of induction highlighting the importance of hypoxia as a pathogenetic factor in brain tumors. This may contribute to maintain the pH gradient with alkaline intracellular and acidic extracellular pH observed in brain tumors. Since powerful inhibitors of carbonic anhydrases are clinically available, CA IX and XII may be an important target for future treatment of brain tumors.

Anti-EGFR monoclonal antibody Cetuximab augments radiation and chemotherapeutic effects in glioblastoma multiforme *in vitro* and *in vivo*.

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Objective: We previously demonstrated that anti-EGFR monoclonal antibody Cetuximab was effective against EGFR-amplified glioblastoma multiforme (GBM) cells in vitro and in vivo. This work examines the combination of Cetuximab with radiation or chemotherapy.

Methods: Cells were implanted intracranially to verify whether Cetuximab crosses the blood brain barrier. To determine the efficacy of Cetuximab on increasing tumor burden, mice with different size flank GBM were used. Finally, mice with flank GBM were exposed to Cetuximab alone, or in combination with radiation. EGFR-amplified GBM lines were also exposed to Cetuximab and chemotherapeutic agents in vitro.

Results: Cetuximab treated-mice had a significant increase in median survival when compared to sham-treated mice for both intracranial and flank tumor models. The inhibition of tumor growth obtained with Cetuximab in mice with flank GBM was inversely proportional to tumor size at the beginning of treatment. Tumor cells undergoing apoptosis was greater upon exposure to Cetuximab and radiation than with either treatment alone. The combination of Cetuximab and radiation treatment increased median survival in mice with flank GBM compared to either treatment alone. The combination of Cetuximab and chemotherapeutic agents increased cytotoxicity in vitro when compared to either treatment alone.

Conclusions: The effectiveness of Cetuximab as a solo agent is dependent upon tumor burden. Cetuximab was effective when administered systemically for mice harboring intracranial GBM. Cetuximab plus radiation was more effective against EGFR-amplified GBM than either treatment alone. Cetuximab in combination with chemotherapeutic agents had an additive effect in vitro. These results confirm EGFR blockade as a potential chemotherapeutic treatment against human GBM.

Multicentric phase III study on fluorescence-guided resection of malignant gliomas with 5-ALA: Preliminary results on interim analysis of 270 patients

Walter Stummer[1], T Meinel[2,3], ALA- Glioma Study Group*, U Pichlmeier[4], OD Wiestler[5], FE Zanella[6], HJ Reulen[3]

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Objective: 5-Aminolevulinic acid (5-ALA) leads to the accumulation of fluorescent porphyrins in malignant gliomas, a phenomenon under investigation for the enhancement of tumor resection. In order to determine patient benefit in terms of resection radicality, progression-free survival and morbidity, a pivotal two-armed, randomized, group-sequential, blinded-observer trial was designed together with the sponsor Medac. This paper gives preliminary results of the interim analysis on the first 270 patients in the full analysis set (intent-to-treat principle population).

Methods: Patients with suspected malignant gliomas bearing the potential for complete resection of contrast-enhancing tumor were randomized to receive either 20 mg 5-ALA/kg body weight for fluorescence-guided resection (ALA-group) or nothing for conventional microsurgery (white light group). Surgery was performed using identical microscopes (Zeiss OPMI Neuro FI) available to each participating center. Primary study aim was to determine the number of patients without contrast-enhancing tumor on early postoperative MRI and progression free survival at six months.

Results: Postoperative MRI was devoid of residual, contrast-enhancing tumor in 65 % of patients in the ALA group compared to 36 % in the white light group ($p < 0.001$). Preliminary Kaplan-Meier analyses revealed prolonged progression-free survival in ALA patients ($p < 0.01$ compared to white light) with cumulative 6-months progression-free survival rates of 41% and 21%, respectively. Median survival was significantly prolonged in patients devoid of contrast-enhancing tumor (16 vs. 12 months, $p < 0.001$). Postoperative neurological status and Karnofsky Index did not differ between ALA or white light patients.

Conclusions: Fluorescence-guided resections using 5-ALA allow a larger number of complete resections without endangering patients. Complete resections have a direct impact on overall survival.

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Is Gross Total Resection Sufficient Treatment for Posterior Fossa Ependymomas?

Robert Spetzler[b,d] , L Rogers[a]; J Pueschel[b,c]; W Shapiro[b,c]; S Coons[b,e]; T Thomas[g]; B Speiser[b,f,g]

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This work is supported by grants from Barrow Neurological Institute and from the Foundation for Cancer Research and Education.

All newly diagnosed intracranial ependymoma patients (n=45) treated at our institution from 1983 to 2002 were identified to determine whether gross total resection (GTR) alone serves as definitive treatment and to evaluate the role of radiation therapy (RT) after either GTR or subtotal resection (STR). Patients with supratentorial primaries, subependymomas, or neuraxis dissemination were excluded. GTR was accomplished in 32 (71%) and STR in 13 (29%). RT was delivered to 25 patients: 13 after GTR and 12 after STR. RT fields were craniospinal followed by a posterior fossa boost in 6, and posterior fossa or local only in 19. With a median follow-up of 66 months, the median local control (LC) was 73.5 months with GTR alone, but has not yet been reached for GTR+RT patients. Median LC after STR+RT was 79.6 months. Ten-year actuarial LC (10y-LC) was 100% for GTR+RT, 50% for GTR alone, and 36% STR+RT, representing significant differences between GTR+RT and GTR alone (p=0.018) and between GTR+RT versus STR+RT (p=0.003). There was no significant difference in 10y-LC between GTR alone and STR+RT (p=0.370). The 10-year overall survival rate of GTR+RT was 83%, 67% for GTR alone, and 43% for STR+RT. RT, tumor grade, and resection extent were significant predictors of LC. GTR should be the intent of surgery when feasible with acceptable morbidity. Even after GTR confirmed with postoperative imaging, adjuvant RT significantly improved LC. We recommend postopera

Mangement of optic nerve sheath meningiomas

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Objective: The management of optic nerve sheath meningiomas (ONSM) remains controversial, but includes surgery, radiotherapy and plain observation. We introduce a new classification scheme and derive treatment modalities from the different types and subtypes.

Methods and Results: A retrospective analysis was performed on 73 patients with optic nerve sheath meningiomas who underwent surgery between 1991 and 2002. The follow-up period ranged from between 6 to 144 months (mean 45.4 mo). Our classification system differentiates between intraorbital (type 1), intracanalicular or intrafissural (type 2), and intraorbital and intracranial (type 3) types of ONSMs. 32 tumors demonstrated extension through the optic canal (type 2a). 29 further tumors reached the chiasm (type 3a) or contralateral side (type 3b). Intraorbital flat tumors (type 1a) should be radiated with visual decline. Type 1b tumors with a large intraorbital mass should be observed, radiated with visual decline, and operated on without useful vision. Only type 1c tumors with exophytic tumor growth should undergo excision. Type 2 tumors are amenable to decompression to save vision and type 3 tumors are amenable to resection of the intracranial part. The intraorbital part should be radiated. The visual acuity was not significantly influenced by surgery. Visual acuity became worse with longer duration of preoperative symptoms and longer follow-up period. Location in the optic canal was another negative factor. Radiotherapy could preserve vision in 5 out of 10 cases.

Conclusions: Loss of vision in optic nerve sheath meningiomas is a question of time. The role of radiotherapy has to be reevaluated and offered to adults once mild vision loss develops in intraorbital ONSMs. Surgery with decompression of the optic canal and intracranial tumor resection is favored for tumors with intracanalicular and intracranial extension.

TUESDAY, OCTOBER 5 **6:30-6:45 pm**

The Role of Endogenous Growth Hormone-Releasing Hormone (GHRH) in Acromegaly

William F Chandler, EV Dimaraki, AL Barkan, MB Brown, V Padmanabhan, SY Kim, R Taussig

There is indirect evidence suggesting hypothalamic control of GH secretion in acromegaly. To examine whether GH secretion in acromegaly is dependent on GHRH, we studied 8 patients with classic untreated acromegaly due to a GH producing pituitary tumor. All patients were admitted to the General Clinical Research Center and underwent an intravenous infusion of normal saline for 24 hours and GHRH-antagonist at 50 g/kg/h for 7 days. GH was measured every 10 min for 24h during the normal saline infusion and on the last day of the GHRH- antagonist infusion. A group of 9 different patients with untreated acromegaly served as the control group and underwent blood sampling for GH every 10 min for two consecutive 24h periods to assess the day-to-day variability of GH secretion. All 8 study patients underwent transsphenoidal surgery and RNA was extracted from the each tissue specimen and tested for gsp mutations.
In 6 of 8 experimental subjects 24h mean GH decreased by 5.8-30.0 % during GHRH-antagonist infusion and in 3 of 8 subjects the decline of the 24h mean GH was greater than twice the average Coefficient of Variation in the control group. The probability of this magnitude of change to occur in 3/8 subjects by chance is 0.0058. Although 3 of 8 subjects were found to have gsp mutations (2 at site R201, 1 at site R227), no relationship was noted between the presence of gsp mutation and GH suppression with GHRH- antagonist.
We conclude that in a subset of patients with acromegaly due to a pituitary adenoma, GH secretion is under partial control by GHRH.

NOTES:

WEDNESDAY PROGRAM

WEDNESDAY, OCTOBER 6 **9:15-9:30 am**

Selection of the optimal entry zone to the brain stem for removal of intraaxial cavernous angiomas

Helmut Bertalanffy

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Objective: Cavernous malformations located within the brainstem show a substantially higher propensity for bleeding than those in other locations. Since radiosurgery appears to be inappropriate for prevention of bleeding, microsurgical removal of brainstem cavernomas is the favored therapeutic option. To completely remove an intraaxial cavernoma without additional morbidity, however, an individually tailored specific entry zone to the brainstem is required, particularly in those cases, in which the lesion is not visible on the surface of the brainstem.

Patients and Methods: During the past 7 years we have treated surgically 56 individuals who harboured - with one exception – a symptomatic brainstem cavernoma. Fourteen of the lesions were located in the midbrain, 36 in the pons and 6 in the medulla. The patient's records, pre- and postoperative images and surgical video tapes were analysed. To obtain an optimal surgical window and viewing trajectory to the brainstem, we carefully selected the surgical approach in each single case. Intraoperative electrophysiological monitoring was used in all, neuronavigation in the majority of patients.

Results: The surgical approaches included the pterional/orbitozygomatic, the subtemporal transtentorial, the retrosigmoid, the suboccipital lateral transcondylar, the supracerebellar infratentorial and the suboccipital median telovelomedullary routes. The lesion itself or the bulging hematoma with xanthochromic coloration was seen in 30 cases, while an apparently normal brainstem was found in 26 cases. In the latter, the brainstem was incised at a site where the shortest distance to the lesion was suspected and confirmed by neuronavigation. The exact site, however, was slightly modified when direct electrical stimulation dictated a different safe entry zone to the brainstem. Postoperatively, 9 patients (16 %) showed transient additional neurological deficits whereas 6 individuals (11 %) experienced permanent neurological morbidity, of whom four are completely independent. One patient died from a disease unrelated to the cavernous malformation. The remaining patients of this series were either in the same neurological condition or improved.

Conclusions: A carefully planned and individually tailored approach was essential to obtain a specific exposure of the brainstem which depended upon the size and exact location of the lesion. The optimal entry zone to the brainstem was based on precise anatomical criteria, on the local vascular pattern, on electrophysiological mapping and neuronavigation. In combination with modern neuroanesthesia and advanced microsurgical techniques, excellent results have been achieved with this method.

WEDNESDAY, OCTOBER 6 **9:30-9:45 am**

The Transgenic Arteriovenous Fistula in the Rat: An Experimental Model of Gene Therapy for Brain Arteriovenous Malformations

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Objective: To introduce the transgenic arteriovenous fistula (AVF) model in the rat, constructed by interposing mouse aorta in a fistula between the common carotid artery and external jugular vein in a nude rat; to describe the model's technical feasibility, long-term patency, and expression of reporter genes.

Methods: Carotid-jugular fistulas were surgically created in 112 rats. In 25 immunodeficient nude rats, wild-type mouse thoracic aorta (TAo) was interposed in the fistula; in 10 immunocompetent rats, TAo was interposed; in 19 nude rats, transgenic TAo with reporter genes for beta-galactosidase (lac-Z) or green fluorescent protein (GFP) was interposed; in 18 nude rats, wild-type mouse ascending aorta (AAo) was interposed; and in 40 rats, a simple fistula was constructed without an interposition graft. Host tolerance and graft viability were determined by histopathology and immunohistochemistry for CD31 (mouse endothelial cell marker), endothelial nitric oxide synthase (eNOS), smooth muscle actin, fibronectin, beta-galactosidase, and GFP.

Results: The transgenic AVF was technically feasible and immunologically tolerated in nude rats, but not in immunocompetent rats. The overall angiographic patency rate was 41% with TAo grafts and 56% with AAo grafts, both lower than the 98% patency rate in fistulas with a single anastomosis and no interposition graft. Mouse endothelium survived on the graft for 3 months according to CD31 staining, but longer survival by transgenic smooth muscle cells resulted in continued expression of lac-Z for 6 months and GFP for 4 months. Endothelium and smooth muscle in the fistula were functional, with normal expression of eNOS, and smooth muscle actin and fibronectin, respectively.

Conclusion: The transgenic arteriovenous fistula model enhances other carotid-jugular fistula models by integrating transgenic tissue, thereby creating an experimental system for investigating the molecular biology of and gene therapies for arteriovenous malformations.

A role for EphB4 signaling in the regulation of vascular morphogenesis and vascular permeability in malignant glioma

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Objective: Several endothelial-specific receptor tyrosine kinases (RTKs) and their ligands have been implicated in glioma angiogenesis. Recently, members of the Eph-group of RTKs (Ephs) and their ligands (ephrins) have been suggested to be involved in developmental angiogenesis and embryonal vascular differentiation. The role of ephrin/Eph signaling in adult angiogenesis, however, has remained unknown so far. The objective of the present study was to assess the role of ephrin/Eph signaling for glioma biology.

Methods: Expression of ephrins and Ephs was assessed in glioma cell lines, human glioma xenografts as well as low- and high-grade human astrocytoma using c-DNA-array analysis, RT-PCR and in-situ hybridization. To further study the role of EphB4 signaling for glioma angiogenesis we used Phoenix E cells producing (i) ecotropic retroviral constructs for EphB4-WT, (ii) EphB4-DN, i.e. a truncated dominant-negative mutant form of EphB4 lacking the kinase domain, and (iii) Phoenix E cells producing an empty vector (mock). Phoenix E cells were co-implanted with glioma cells into flanks or the dorsal skinfold chamber preparation of nude mice. Glioma angiogenesis and glioma growth were assessed by immunohistochemistry and intravital multi-fluorescence videomicroscopy.

Results: Expression of several ephrins (EphrinA1, EphrinB1, EphrinB2) and Ephs (EphA2, EphA5, EphB2, EphB3, EphB4) could be detected in human gliomas. Compared to normal brain, expression of EphB4, EphB3 and EphrinB2 mRNA was increased in glioma, whereas expression of EphA5 and EphA2 mRNA was reduced in glioma. Interestingly, expression of ephrins and Ephs in glioma xenografts was detected on both blood vessels and tumor cells. In situ hybridization of human astrocytoma specimens further demonstrated that, while ephrinB2 was homogeneously expressed by tumor cells and tumor blood vessels, EphB4 mRNA was predominantly expressed by perinecrotic tumor cells and tumor blood vessels. Based on these results we next set out to study the role of EphB4 signaling for glioma angiogenesis in detail. *In vivo* manipulation of endothelial EphB4 signaling with EphB4-WT and EphB4-DN constructs did not affect initial sprouting tumor angiogenesis, but markedly altered the vascular phenotype of the tumors. Compared to mock tumors, both EphB4 WT- and EphB4-DN tumors were characterized by a rather circumferential than branching vessel growth, resulting in extremely large (>200µm) tumor vessels, and by a significant reduction in tumor vessel permeability.

Conclusion: The results demonstrate that CA IX and XII are upregulated in intrinsic and metastatic brain tumors compared to normal brain tissue. Hypoxia seems to be the major mechanism of induction highlighting the importance of hypoxia as a pathogenetic factor in brain tumors. This may contribute to maintain the pH gradient with alkaline intracellular and acidic extracellular pH observed in brain tumors. Since powerful inhibitors of carbonic anhydrases are clinically available, CA IX and XII may be an important target for future treatment of brain tumors.

Gamma Knife Radiosurgery in the management of glomus tumors – a volumetric study of 17 Cases

Gene H Barnett, A Varma, JH Suh, J Ross

Twenty patients with glomus jugulare tumors underwent Gamma Knife radiosurgery (GKRS) at the Cleveland Clinic during a 6-year period from 1997 to 2002. Three patients with follow up of less than 10 months were excluded. Clinical and radiological data from 17 patients were retrospectively analyzed. MRI tumor volumes at treatment and follow-up were assessed.

There were 15 women and 2 men, with an average age of 63.1 years (range 22 to 87). Follow up was 10 to 79 months (average 44.5 months). Six patients had undergone previous surgical resection of the same tumor, two had multiple tumors and one had a functional chemodectoma. Symptoms were tinnitus (n=12), hearing loss (n=12), lower cranial nerve paresis (n=6) and otalgia (n=5). Tumor margins received 13 to 18 Gy (average = 15 Gy, median = 15 Gy) at 48% to 63% (average = 53%, median = 50%) isodose line. Eight patients clinically improved, 2 patients worsened and 7 patients were unchanged. One patient experienced transient hearing impairment. Tinnitus and otalgia responded most favorably to GKRS. Initial tumor volumes ranged from 0.4 to 26.1 cm3. Tumor volume showed a transient increase in 7 patients though ultimately decreased in 8 patients (4 clinically improved, 3 unchanged & 1 worse), increased in 4 patients (2 clinically unchanged, 1 improved, 1 worse) and was unchanged in 5 patients (3 clinically improved and 2 unchanged).

GKRS is a safe, effective treatment for glomus jugulare tumors, particularly in elderly patients and patients with serious medical conditions.

Intraoperative Functional MRI. First results and technical considerations.

Thomas Gasser[1], D Stolke[1], R Fahlbusch[2], C Nimsky[2]

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Objective: The preservation of eloquent cortex during a neurosurgical intervention is essential for the functional outcome.
Functional MRI represents an established concept to map functional units. However, fMRI paradigms are generally active in nature, limiting the method to awake and cooperative patients and to the preoperative period. However, a novel passive fMRI paradigm for localization analysis of the sensorimotor cortex allows functional analysis of neurologically impaired or anaesthetized patients. The paradigm is based on peripheral electrical nerve stimulation during echo-planar image acquisition. Preceding studies have already established clinical applications of this fMRI-paradigm.
The present prospective study evaluates the feasibility of true intraoperative fMRI utilizing this paradigm in anaesthetized patients undergoing brain tumour resection. The study focused as well on the technical setup and the intraoperative management.

Methods: In 3 anaesthetized patients with centrally localized lesions intraoperative fMRI scans were acquired at 3 distinct stages of the surgical procedure employing an intraoperative 1.5 Tesla MR scanner. The data were analyzed statistically and co-registered with the Talairach space. Additionally the data were validated by electrophysiology.

Results: Utilizing this passive fMRI paradigm, the sensorimotor cortex could be identified intraoperatively in 2 of the 3 patients. We observed a significant change in signal intensity in the course of the operation and detected regularly an inverted BOLD-signal response, which may be caused by an inhibition of cerebrovascular autoregulation under total intravenous anaesthesia (TIVA). Susceptibility artefacts influenced image quality marginally.

Conclusion: We could demonstrate the feasibility of this method to identify the sensorimotor cortex in anesthetized patients in the surgical setup. Further studies will have to evaluate the BOLD-signal characteristics under anaesthesia and the clinical impact of intraoperative fMRI.

Sirolimus-eluting Stents in the Canine Cerebral Vasculature: Assessment of Safety Profile and Vessel Response

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Purpose: The treatment of intracranial atherosclerosis with bare-metal stents results in excessive restenosis rates. Neurotoxicity effects and vessel injury following implantation of drug-eluting stents are unknown in the cerebrovasculature. To assess the safety and vascular effects of sirolimus-coated stents, we conducted a prospective comparison study of drug-eluting and bare metal stent implantation in the canine basilar artery.

Method: Sixteen mongrel dogs were randomized to receive either bare metal 1.5- x 8-mm (6-cell) stents or sirolimus-eluting stents of the same dimensions. Serial peripheral blood samples were obtained during the first week after stent implantation to determine the time-dependent serum sirolimus concentration. Angiograms were performed 30 days post-implantation to assess the effects of stent placement on the basilar artery and brainstem perforators. Stent and basilar artery explantation was performed immediately after angiography. Histological and computer-assisted morphometric analyses of specimens obtained were performed.

Results: No sirolimus was detected in peripheral blood samples obtained later than 24 hours post-treatment. On follow-up angiography, no evidence of parent vessel damage or pseudoaneurysm formation was seen. Explanted vessels and brainstem sections showed no evidence of neurotoxicity. No significant differences were found in the time to endothelialization of bare-metal and sirolimus-coated stents. Smooth-muscle cell proliferation was lower in animals receiving sirolimus-coated stents ($p = 0.003$). Additionally, intimal fibrin density was increased in the group treated with sirolimus-coated stents ($p < 0.0001$). Histological evidence of an inflammatory response indicated a trend toward a reduced response in the sirolimus group.

Conclusion: These findings suggest that sirolimus-coated stents may inhibit in-stent stenosis. Further studies with longer-term follow-up are required to assess the restenosis rates of sirolimus-coated stents implanted in intracranial vessels.

Brain tumour surgery in the vicinity of short-term memory representation – results of neuronavigation using fMRI images.

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Objective: Functional informations concerning the surrounding brain are mandatory for a good clinical outcome in brain tumour surgery. The value of fMRI to detect the motorcortex and the Broca area is widely accepted today. If an appropriate paradigm is used, short-term memory areas can be visualized as well. Obviously these informations must be integrated into cranial neuronavigation for an appropriate intraoperative use. We report our first experiences with the direct integration of short-term memory fMRI into cranial neuronavigation.

Method:. From January 2001 to March 2002 14 patients were operated on for intracranial tumours with short-term memory fMRI imaging, using the „two-back-paradigm". Both pre- and postoperatively, the short-term memory of all patients was tested additionally by a standardized test battery including 16 different verbal and visuo-spatial items. FMRI was repeated postoperatively as well.

Results: In all 14 patients the general level of working memory capacity was preserved after surgery and we found an improvement in verbal short-term memory items. In contrast, the visuo-spatial performance kept unchanged or deteriorated slightly and the alertness slightly worsened as well.

Conclusion: Functional fMRI basing on a short-term memory paradigm is able to improve the outcome after surgery for cortical and subcortical brain tumours localized in the frontal and precentral area. The so-called two-back paradigm mainly serves for verbal memory tasks. For visuo-spatial items, we are going to design a new paradigm. Unfortunately it has to be mentioned, that irradiation may deteriorate this capacity as well.

Fiber tract deformation as visualized with sequential acquisitions of 3D-ultrasound (3DUS) during intracranial surgery

Volker A Coenen, T Krings, J Weidemann, FJ Hans, P Reinacher, JM Gilsbach, V Rohde

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Objective: We present a technique that intraoperatively allows displaying brain shift and its effects on fibre tracts that preoperatively were studied with diffusion-weighted imaging (DWI). With DWI the pyramidal tract and the optic radiation can be displayed among other fiber tracts. Intraoperative 3D – ultrasound (3DUS) has the ability to directly compare ultrasound and MRI (or DWI) anatomy. 3DUS cannot directly visualize fiber tracts in the white substance of the brain. However, it is possible to estimate a fiber tract's position by defining an environment of ultrasound landmarks on the basis of the US – DWI comparison.

Methods: In three patients intracranial lesions (1 malignant glioma, 1 metastasis, 1 cavernoma) with contact to either the corticospinal or the geniculostriate tracts were removed microneurosurgically. Preoperatively, diffusion weighted magnetic resonance imaging (DWI) was obtained to visualize the fiber tract at risk. DWI data were fused with the anatomical T1-weighted magnetic resonance (MR) image. A single rack 3D - ultrasound (3DUS) neuronavigation system, which displays simultaneously the MR image and the corresponding ultrasound image was used intra-operatively for 1) navigation 2) definition of fixed and shiftable ultrasound-landmarks in vicinity to the fiber tract 3) sequential image update at different steps of resection resulting in time dependent brain deformation data. Using a standard personal computer equipped with Windows®-based image software, the brain shift-associated fiber tract deformation was assessed by sequential landmark registration. After surgery, DWI was obtained to directly confirm the predicted fiber tract deformation.

Results: The lesions were removed without any morbidity. The comparison of 3DUS with DWI and T1-weighted MRI allowed to define fixed and shiftable landmarks close to the respective fiber tract. Postoperative DWI confirmed, that the actual fiber tract position corresponded to the sonographically predicted fiber tract position at the end of surgery.

Conclusion: By definition and sequential intraoperative registration of ultrasound landmarks in vicinity to a fiber tract, brain shift associated deformation of the sonographically not visible tract can be correctly assessed. This approach appears to be helpful to identify and avoid eloquent brain during intracranial surgery.

German Society First Prize Award (Wilhelm Tönnis Preisträger)

Mechanical Response of a Cervical Spine Motion Segment on Removing a Local Autograft

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Objective: There is evidence, that filling a cervical spine fusion cage with either bone substitute or autologous bone graft from the iliac crest is beneficial with respect to speed and rate of the bony fusion. However, both bone substitutes and the iliac crest autograft have specific disadvantages. Using a local autograft from the cervical spine vertebral bodies to fill a cervical spine fusion cage might be an alternative. However, removing the local autograft from the vertebral bodies of the cervical spine could result in reduced strength of the spinal segment, thus again leading to severe complications. Therefore, mechanical testing of such a procedure should be performed before the method is to be used in clinical practice.
The objective of the study was to investigate, if removing a local autograft from the cervical spine vertebral bodies significantly reduces compression strength of a cervical spine segment.

Methods: 14 human cervical spine segments (C4-C5 and C6-C7) were used. According to bone mineral density they were assigned to either control or test group. Each specimen underwent anterior discectomy and insertion of a titanium cage (Rabea, Signus Medizintechnik, Alzenau). Within the specimen, assigned to the test group, a cylindrical bone dowel of 5 mm depth and 5 mm diameter was removed from the anterior aspect of each vertebra. The specimens were then loaded in flexion-compression. We looked at the force resulting in the first failure, at the force resulting in 4 mm displacement of the construct and at the correlation of these parameters to the bone density of the segment.

Results: Then mean force resulting in initial failure was 1149 N for the test and 1647 N for the control group ($p = 0,252$). The force resulting in 4 mm displacement was 1064 N for the test and 1574 N for the control group ($p = 0,155$). There was a strong and significant correlation of these parameters versus bone density for the control group, however, the correlation was moderate and not significant within the test group.
Conclusion: Removing a cylindrical dowel of 5 x 5 mm from the anterior aspect of the cervical spine vertebral bodies does result in a not significant reduction of strength in flexion-compression.

American Academy Honorable Mention Award

Selective ablation of vanilloid receptor 1 positive nociceptive neurons for elimination of hyperalgesia and neuropathic pain.

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Objectives. Neuropathic pain is mediated by nociceptive neurons that selectively express the vanilloid receptor 1 (VR1). Resiniferatoxin, an excitotoxic VR1-agonist, destroys VR1-positive neurons. To determine if resiniferatoxin can selectively ablate VR1-positive neurons and eliminate neuropathic pain without affecting tactile sensation and motor function, we infused it unilaterally into primate trigeminal ganglia.

Methods. We perfused resiniferatoxin (experimental=3) or vehicle (control=1) into the right trigeminal ganglia of Rhesus primates and tested tactile and hyperalgesic sensation in trigeminal-innervated territories (corneal application of saline and capsaicin, respectively) at 1, 4 and 7 weeks postoperatively. Number of blinks, eye wipes, and duration of squinting were recorded after application. Neurogenic inflammation, mediated by VR1-positive neurons, was tested by facial application of capsaicin cream. Immunohistochemical analyses were performed after euthanization.

Results. Consistent with elimination of hyperalgesia on the side of resiniferatoxin-treated ganglia, there was a dramatic reduction in the number of blinks (mean±S.D.; 25.7±4.4 versus 106±20.8, and 112.8±19.7), eye wipes (1.4±0.8 versus 19.3±5.0 and 16.7±4.5), and duration of squinting (1.4±0.7 seconds versus 11.4±1.6 and 14.8±1.7) in response to corneal application of capsaicin, compared to the vehicle and untreated sides, respectively ($p<0.01$). Tactile sensation (mean blinks after saline application; 18.8±2.3, versus 18.0±2.6, and 18.4±3.3, respectively; $p>0.05$) and motor function (mastication) remained intact. Neurogenic inflammation was blocked on the resiniferatoxin-treated side. Animals showed no adverse clinical effects. Immunohistochemical analysis revealed selective ablation (mean decrease, 79.3±2.8%; $p<0.001$) of VR1-positive neurons in the resiniferatoxin-treated ganglia.

Conclusions. VR1-positive nociceptive neurons can be safely and selectively ablated by intraganglionic resiniferatoxin infusion, eliminating hyperalgesia and neurogenic inflammation while maintaining intact tactile sensation and motor function. Intraganglionic resiniferatoxin infusion could provide a new site-specific, mechanism-based treatment approach for neuropathic pain.

German Academy First Prize Award

Identification of Brain Tissue Necrosis by MRI: Validation by Histomorphometry

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The volume of an experimental necrotic lesion of the cortex expands up to 400 % of its initial size within the first 24 hrs after the insult. Lesion expansion, a clinically well known phenomenon, is often accompanied by perifocal brain edema and consequently difficult to image and to analyze by magnetic resonance imaging (MRI). Therefore we aimed to validate a T_2-weighted spin echo sequence upon its ability to distinguish necrotic from edematous brain tissue.

Male Sprague-Dawley rats (n=5 per group) were subjected to a cortical freezing lesion leading to immediate tissue necrosis with subsequent perifocal vasogenic brain edema. Immediately, 4, 12, and 24 hrs after the lesion the maximal area of necrosis was quantified longitudinally by coronal T_2-weighted spin echo MRI-scans. After the last scan, animals were sacrificed for direct comparison of the lesion area obtained by MRI and histomorphometry. In parallel groups of animals, lesion expansion was quantified by histology.

The acquired T_2-maps clearly distinguish the cortical necrosis from perifocal edema and healthy brain. Focal freezing led to a cortical lesion of 5.24 ± 0.36 mm^2 immediately after trauma (0 h; 100 %) which expanded progressively to a maximum of 6.82 ± 0.34 mm^2 after 24 hrs (131 %; * $p<0.01$ vs. 0h). Lesion expansion quantified by histology was almost identical (132 % within 24 hrs). Histological assessment resulted in smaller absolute lesion areas compared to MRI, most likely due to shrinking during tissue processing (4.72 ± 0.26 mm^2 vs. 6.82 ± 0.34 mm^2, $p<0.01$).

The current study shows that necrotic brain tissue can be distinguished from surrounding brain edema by T_2-mapping. The technique is sensitive enough to detect small changes in necrosis expansion in vivo as validated by histology. The presented technique may be a useful future tool for the non-invasive identification of necrotic brain tissue following brain injury, e.g. from trauma or ischemia.

American Academy First Prize Award

Achieving a Multidimensional brain computer interface in humans using electrocorticographic signal

Eric C. Leuthardt, G Schalk, JR Wolpaw, JG Ojemann, DW Moran

Brain-computer interfaces (BCIs) enable users to control devices with electroencephalographic (EEG) activity from the scalp or with single-neuron activity from within the brain. Both methods have disadvantages: EEG has limited resolution and requires extensive training, while single-neuron recording entails significant clinical risks and has limited stability. This research demonstrates that electrocorticographic (ECoG) activity recorded from the surface of the brain can enable users to control a computer cursor rapidly and accurately. Previously, over brief training periods (several minutes), four patients mastered control and achieved high success rates in one dimensional tasks. In additional experiments, we found that ECoG signals at frequencies up to 180 Hz accurately reflected the direction of two-dimensional joystick movements. These techniques derived to achieve one dimensional control were then used to translate this to two dimensional control in one patient with success rates of 70-94%. These results suggest that an ECoG-based BCI could provide people with severe motor disabilities a non-muscular multidimensional communication and control option that is more powerful than EEG-based BCIs and is significantly easier and safer than BCIs that use electrodes penetrating the brain.

NOTES:

THURSDAY PROGRAM

THURSDAY, OCTOBER 7 **9:15-9:30 am**

Clinical outcome following Transforaminal Lumbar Interbody Fusion (TLIF): One year follow-up of prospective data.

Richard G. Fessler

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METHODS: Two studies were completed using a prospective, non-randomized design.
Study 1: 50 patients underwent either open TLIF or minimal access TLIF (MAST TLIF). 25 patients were in each group. All patients receiving open TLIF were performed by one surgeon, and all MAST TLIFs were performed by a second surgeon. Surgeries were performed over the same period of time. Data collected included age, sex, levels operated, operative time, blood loss, transfusions, pain medications received, and length of stay. Results were analyzed using Wilcoxon Signed Rank analysis and Student's t-test analysis.
Study 2: 56 patients who were scheduled to undergo MAST TLIF were pre-operatively administered VAS, Oswestry Disability Scale, and SF-36 questionnaires. Surgery was then performed and the same tests were re-administered at 6 wks, 4 ½ months, and 1 year post-operatively. Data at 1 year was compared to the pre-operative data using the Wilcoxon Signed rank analysis for VAS scores and repeated measures ANOVA for the Oswestry Disability Scores and SF-36 scores.

RESULTS: Study 1: Patient demographics, including age and levels operated were not significantly different. More males were done through mast technique than open. Operative time was not significantly different between the groups. Patients undergoing MAST TLIF lost significantly less blood (200 v 1100 cc, $p < .002$), required significantly fewer transfusions (0 v 33 %, $p < .001$), and took significantly less pain medicine (130 v 180 MSO4 equivalents, $p < .05$). Length of stay was less for MAST TLIF patients, but did not reach statistical significance.

Study 2: Patients followed for 1 year after MAST TLIF experienced a 98 % fusion rate. Visual analog scores decreased from 5.5 to 3.5 ($p < .008$). Oswestry disability scores decreased from 45 to 30 ($p < .0001$), and SF-36 scores for physical functioning increased from 35 to 46 ($p < .01$).

DISCUSSION: The MAST TLIF technique for performing lumbar interbody fusion and stabilization is a safe and effective procedure. In similar groups of patients it can be performed in the same or less time than open procedures, while causing less blood loss, fewer blood transfusions, and requiring less pain medicine and possibly shorter hospital stays. Long term follow-up demonstrate significant improvement in pain, disability, and overall satisfaction with life compared to pre-operative values.

Application of Image-Guided Spinal Navigation to Decompression and Internal Fixation of the Upper Cervical Spine

Iain H. Kalfas

Cleveland Clinic Foundation

The techniques for decompression and internal fixation of the upper cervical spine have evolved significantly. This has resulted from an improved understanding of spinal biomechanics, improvements in spinal imaging, the refinement of surgical exposure techniques as well as continued advances in the design of internal fixation devices.

Despite these advances, the anatomic complexity of the upper cervical region can present difficulties for even the most experienced spinal surgeons. In particular, orientation to the pertinent neural, vascular and bony structures is critical to optimizing the outcome of surgery. While intraoperative fluoroscopy can help facilitate anatomic orientation, it has several technical limitations.

Computed tomography-based image-guided spinal navigational technology has evolved over the past decade. Unlike, fluoroscopy, it provides the surgeon with multiplanar images through the upper cervical region. These images can be manipulated intraoperatively to provide enhanced orientation to the surgical anatomy.

Forty patients underwent surgery for decompression and internal fixation of the upper cervical spine using image-guided spinal navigation. Thirty-two patients underwent posterior C1-2 screw fixation, 5 patients underwent transoral surgery with posterior C1-2 screw fixation and 3 patients underwent anterior odontoid screw fixation. Fluoroscopy was also used on a limited basis during each case to validate the navigational information.

Satisfactory screw placement was achieved in all patients. There were no incidences of neural of vascular injury due screw placement. The technique of using image-guided technology for upper cervical surgery will be reviewed.

Laboratory testing of an implantable microsensor system for intraoperative 3D-computer animation of vertebral body motion in cervical spinal surgery

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Objective: Degenerative diseases of the cervical spine may not only cause neurological deficits due to direct compression of the spinal cord or the spinal nerves, but also alter its biomechanical function and statics. In such cases, the aim of surgery is double: to decompress neural structures and to provide the highest possible stability and the best possible preservation of function. Regardless of the surgical technique used, intraoperative prediction of the functional (neurological and biomechanical) results of surgery, might represent a major progress.

Materials & Methods: Navigationsystems have been used in spinal surgery for specific surgical planning, optimization of anatomical orientation and improvement of surgical accuracy. In the present research project (sponsored by the Deutsche Arthrose Hilfe e.V.), reference sensors of an electromagnetic navigation system (ACCISS II™, Schaerer Mayfield Technologies) have been miniaturized for direct implantation into one or more vertebral bodies with the aim of providing precise additional spatial online information on the location of the vertebral bodies and their orientation in space. In laboratory tests, up to three microsensors were implanted into several cervical vertebrae of cadaver specimens.

Results: Five different surgical techniques (ventral fusion, dorsal fixateur implantation, ventrolateral plate osteosynthesis, foraminotomy, cage implantation) were performed in a total of ten cervical spine models using different segments (C1-3, C5/6, C6-T1). The isolated vertebral body movements were registered and visualized online on the navigation screen.

Conclusion: The implanted reference sensors allow computer-animated, real-time visualization of isolated movements of individual vertebral bodies or of entire motion segments. This means that motion can be visualized immediately during surgery without the need for additional intraoperative imaging procedures such as fluoroscopy or computed tomography. These results indicate that reliable information on the expected postoperative biomechanical outcome can be obtained by continuous intraoperative three-dimensional animation.

THURSDAY, OCTOBER 7 **10:00-10:15 am**

Transthoracic discectomy without interbody fusion

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Object: Transthoracic discectomy is an established surgical procedure for the treatment of thoracic disc disease. Most authors advocate interbody fusion following transthoracic discectomy. The purpose of this study was to determine if there were adverse consequences in forgoing interbody fusion following transthoracic discectomy.

Methods and Results: From 1996 to 2002, the senior author performed transthoracic discectomy without fusion on eighteen patients. There were eleven women and seven men in this series. Their mean age was 54 years (SD=17, range 28-84). Surgical indications were radiculopathy in 1 patient, myelopathy in 14 patients, and radiographic cord compression in 3 patients. We obtained postoperative CT scans to evaluate the decompression in most patients. We obtained followup data from clinic visits and telephone surveys. We obtained and compared pre and postoperative radiographs to determine the incidence of postoperative kyphosis at the operated level. Mean followup was 2.3 years. No patients reported the new onset of axial spine pain postoperatively. Fourteen of 18 patients had significant improvement in neurological symptoms and signs. The only three non-ambulatory patients regained ambulation. One 83 year-old patient had a slight increase in gait difficulties postoperatively. There were three major complications: 1 wound infection, 1 sympathetic pleural effusion requiring pleurodesis, and 1 case of disabling postthoracotomy pain. No patients developed a clinically significant kyphotic deformity.

Conclusions: These results indicate that interbody fusion may not be necessary in all patients undergoing transthoracic discectomy.

Treatment of Spinal Cord Injury via Topical Perfusion with an ATP Solution

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LBE Shields[1], M Li[2], B Chiang[2], DA Burke[1]

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ATP depletion damages ATP sensitive ion channels following spinal cord injury (SCI), leading to membrane failure and cell death. These processes may be reversed by the application of exogenous ATP. ATP solution, stabilized in a lecithin suspension, has been shown to protect hepatic tissue and skin following injury (unpublished data). Besides supporting metabolism, ATP may be trophic in neurogenesis and cell survival by acting on its P2X and P2X receptor subunits. We suggest that exogenous administration of ATP solution to the spinal cord following SCI may prevent irreversible damage and improve functional recovery.

Sixteen Sprague-Dawley rats received a 25 gm-cm SCI at T10 and were assigned into one of two groups: 1) injury/vehicle (control: n = 8) and 2) injury/ATP enhanced solution containing 3000 µmol ATP/ml (n = 8). A perfusion well was designed to irrigate ATP solution to the injured spinal cord. Flow rate was 5 ml/hour for 24 hours. Locomotion was tested weekly for 6 weeks after SCI using the BBB score. At week 6, rats were fixed, and their spinal cords are being assessed for lesion size and tissue preservation.

BBB scores were higher in rats irrigated with the ATP enhanced solution compared to the control group. Locomotor function was significantly better in the ATP-treated groups at 2, 4, and 5 weeks ($p \leq 0.05$). Tissue sparing and lesion size of the spinal cords will be analyzed after 6 weeks.

We conclude that topical application of exogenous ATP provides functional and possibly anatomical neuroprotection following moderate SCI.

"IOMaster 7D" – a new device for virtual neuroendoscopy

Christos Trantakis[1], J Meixensberger[1], G Strauß[2], E Nowatius[3], D Lindner[1], HK Cakmak[4], H Maaß[4], C Nagel[1], U Kühnapfel[4]

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Objective: To create a VR training system for neuroendoscopy. A new force feedback device was intended to be developed and evaluated regarding the suitability for the simulation of endoscopic ventriculocisternostomy.

Methods: A VR model for ventriculostomy was generated based on a MRI dataset. Software modules were used for segmentation (VESUV), modelling (KisMo) and visualization (KISMET) and implemented on a WIN32 platform. Real instruments (MINOP, Aesculap, Germany) were adapted to the simulator. The system was evaluated in 79 procedures.

Results: The "IOMaster 7D" offers 7 degrees of freedom. Both the trocar and the acting instruments are captured separately. The trocar's position determines the view of the camera, the access to the target, and the operating range. An elastodynamic hydrocephalic ventricular system with realistic proportions was modeled. An interactive virtual preparation with force feedback was implemented. The system provides for axial movement or rotation of the instruments, cutting, grasping and realistic elastodynamic deformations of the ventricle wall. First evaluations proved a reduction of the median failure rate and a reduction of the median time to reach the target. Analysis of the total distance of instruments movement showed a reduction, too.

Conclusion: VR systems can simulate realistic and real time surgical procedures and may open new perspectives for the neurosurgical training. Integrating haptic information increases the quality. The definition of no touch areas and targets and the possibility of registration of both kinetic parameters, failure rate and the time course of the procedure provide objective criteria for the appreciation of a learning effect.

THURSDAY, OCTOBER 7 **11:15-11:30 am**

Fedor Krause, The Krause Operations, and Krause's Impact on American Neurosurgeons.

Peter W. Carmel[1], M Buchfelder[2]

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Fedor Krause (1856-1937), the pioneering German neurosurgeon, is widely known and revered in Germany, but is poorly known among American neurosurgeons. He is slightly better known for his innovative cranial approaches; the "Krause operations".

We have assessed Krause's impact on contemporaneous American neurosurgeons by review of references in over 30 books and monographs by Cushing, Dandy, Elsberg, and Frazier. This informal "citation index" permitted comparison with other contemporaneous authors.

Each of the four authors cited Krause frequently, not only from the English translation of his book (1909-1911), but from his papers in German as well. Indeed, Elsbergs' "Surgical Diseases of the Spinal Cord" (1916) cites Krause more often than any other author. Elsberg and Frazier credited Krause with innovation of two further "Krause operations"; a form of osteoplastic laminectomy, and mid-line cord myelotomy for pain.

This generation of neurosurgeons knew German, (the language of science), and several had spent a Wanderjahre in Europe while training. These four American neurosurgeons were clearly highly influenced by Krause's work. Why is he not better known in America today? It may be related to the fact that subsequent neurosurgical generations were less likely to read German, and after 1933, less likely to travel to Germany. They only knew of Krause through his 1911 book, which had been through many revisions in German (68 editions!) but not in English.

We will review the career, surgical innovations, and impact of this unique neurosurgical progenitor, with the hope of wider understanding of his contributions.

Diffusion tensor imaging for 3-D fiber tract visualization in navigated glioma surgery

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Objective: To investigate the intraoperative displacement of major white matter tracts during navigated glioma resection by comparing pre- and intraoperative diffusion tensor imaging (DTI) based fiber tracking.

Methods: In 37 patients undergoing glioma surgery pre- and intraoperative DTI was performed with a 1.5 T magnetic resonance scanner applying an echo-planar imaging sequence with 6 diffusion directions. For 3-D tractography we implemented a knowledge-based multiple-ROI (region of interest) approach applying user-defined seed regions in the color-encoded maps of fractional anisotropy (FA). Tracking was initiated in both retrograde and orthograde directions according to the direction of the principal eigenvector in each voxel of the ROI. The tractography results were also assigned color applying the convention used in color-encoded FA maps. In 15 patients DTI data were integrated into the navigation setup.

Results: Pre- and intraoperative fiber tracking was technically feasible in all cases. Fiber tract visualization gave a quick and intuitive overview of the displaced course of white matter tracts in 3-D space. Comparing pre- and intraoperative tractography depicted a marked shifting of major white matter tracts during glioma removal. Maximum white matter tract shifting ranged from -8 to +15 mm (+2.7 ± 6.0 mm; mean ± standard deviation); in 29.7% an inward, in 62.2% an outward shifting was detected. DTI based neuronavigation allowed identification and preservation of deep seated eloquent brain areas.

Conclusion: Comparing pre- and intraoperative fiber tracking visualizes a marked shifting and deformation of major white matter tracts due to tumor removal. This brain shift of deep structures emphasizes the need for an intraoperative update of navigation systems, when navigation is applied during resection of deep-seated tumor portions near eloquent brain areas.

Changes of the astrocytic matrix and reappearance of radial glia in hippocampi of patients suffering from temporal lobe epilepsy

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Objective: Temporal lobe epilepsy (TLE) is frequently associated with a sclerosis of the hippocampus, also known as Ammon's horn sclerosis (AHS). These hippocampi show a significant neuron loss with astrogliosis. In the recent literature most attention was paid to neuronal changes. However these hippocampi show complex remodelling of synapses and neuronal layers, as a widening of the usually very slim granule cell layer (GCL dispersion) which might be influenced by the change of the glial matrix.

Methods: Hippocampal specimens were obtained from hippocampi of patients treated for pharmaceutically intractable TLE (n=12) and from patients with intracerebral tumours, who served as controls (n=3). The GCL dispersion and the back-grown mossy fibres of the two groups were compared with immunhistochemistry against glial fibrillary acid protein (GFAP) and Silver-Impregnations. The astrocytes were reconstructed and the morphology was evaluated by an optical analysis system (Neurolucida).

Results: Astrocytes proximal to the granule cell layer display a change of their processes. The usually star-like shape of the processes changed into longer processes projecting vertical through the dispersed GCL. Some radial gial cells were observed projecting also vertical to GCL.

Conclusion: Hippocampi of patients with AHS demonstrate a change of the glial scaffold and a new appearace of progenitor cells which project vertical through the GCL along the embryonal sprouting direction of neurons in the hippocampus.

Surgical treatment of hemispheric intractable epilepsy in childhood with functional hemispherectomy or peri-insular hemispherotomy.

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Objective: To present the surgical and clinical results of the therapy of 71 hemispherical intractable epilepsies in children and juveniles, who were operated on in Bethel Epilepsy Centre between May 1990 and August 2003, undergoing either hemispherectomy or hemispherotomy.

Method: We analysed retrospectively these 71 cases. The age at the operation ranged from 4 months to about 17 years (30% aged 3-14 years, 33% 1-3 years and 29% infants). The indication for hemispherectomy was set in 44 cases with congenital etiologies (25 hemimegalencephaly, 14 cortical dysplasia and 5 Sturge-Weber cases) as well as in 27 cases with acquired lesions (11 Rasmussen encephalitis, 13 porencephaly cases after MCA-infarct and 3 other encephaloclastic lesions). By the functional hemispherectomy, the big central region tissue resection was followed from the temporal lobectomy, amygdalohippocampectomy, callosotomy and undercutting disconnection of frontal and occipital lobes. By the hemispherotomy we achieved through smaller craniotomies, shorter operating times and less blood loss, the disconnection of the hemisphere from inside the lateral ventricle. The epilepsy outcome is evaluated according to the Engels classification, with mean follow up of 6 years and 4 months.

Results: 28 patients underwent functional hemispherectomy and 43 patients peri-insular hemispherotomy. The advantages of hemispherotomy are obvious in the porencephalic and the atrophic lesions. The epilepsy outcome is 71 % seizure free or almost seizure free and additionally 17% of cases benefited from the operation (Engels III). The rates of incomplete disconnection have been reduced by the hemispherotomy. 7 % of cases needed a shunt implantation. The mortality was 2,8 %.

Conclusion: The peri-insular hemispherotomy can be safely applied in all etiologies of hemispheric intractable epilepsy and comparable to functional hemispherectomy, has better surgical and clinical results. The early operation is beneficial for the development of the children, taking full advantage of the brain plasticity in this age.

NOTES:

AUTHORS INDEX

Avalox® i.v.
Moxifloxacin

Die Ökonomie der Pneumonie.*

Die Ökonomie von Avalox® i.v.

- Schnell fieberfrei
- Rasche Umstellung von i.v. auf oral
- Verkürzter Klinikaufenthalt (2 Tage)[1]

*ambulant erworbene Pneumonie

Bauer, T., Klinik & Forschung 10 (2004) Suppl. 1: 1-65

Avalox® 400 mg Filmtabletten / Avalox® 400 mg / 250 ml Infusionslösung. Breitspektrum Antibiotikum. Wirkstoff: Moxifloxacinhydrochlorid. **Zusammensetzung:** Arzneilich wirksamer Bestandteil: 1 Filmtablette enthält 436,8 mg Moxifloxacinhydrochlorid, entspr. 400 mg Moxifloxacin. 1 Flasche enthält 1,6 mg / ml (400 mg / 250 ml) Moxifloxacin (als Hydrochlorid). Sonstige Bestandteile: Avalox® 400 mg Filmtabletten: Croscarmellose-Natrium, Lactose-Monohydrat, Magnesiumstearat, mikrokristalline Cellulose, Hypromellose, Macrogol 4000, Eisen(III)-oxid (E 172), Titandioxid (E 171). Avalox® 400 mg / 250 ml Infusionslösung: Natriumchlorid, Salzsäure, Natriumhydroxid, Wasser für Injektionszwecke. **Anwendungsgebiete:** Avalox® 400 mg Filmtabletten: Zur Behandlung von folgenden bakt. Infekt.: akute Exazerbation d. chron. Bronchitis; ambulant erworbene Pneumonie, ausgenommen schwere Formen; akute bakterielle Sinusitis (entsprechend diagnostiziert). Avalox® 400 mg / 250 ml Infusionslösung: Zur Behandlung von folgender bakt. Infekt.: ambulant erworbene Pneumonie, soweit durch Moxifloxacin-empfindliche Bakterien hervorgerufen und initial parenterale Therapie erforderlich. **Gegenanzeigen:** Überempfindlichkeit g. Moxifloxacin, andere Chinolone o. einen der sonst. Bestandteile, Schwangere, Stillende, Kinder, Jugendliche in d. Wachstumsphase, Sehnenerkrankungen/-schäden infolge einer Anwendung von Chinolonen in d. Anamnese. Patienten mit QT-Intervall-Verlängerungen, Störungen des Elektrolythaushaltes, insb. bei Hypokaliämie, klinisch relevanter Bradykardie, klinisch relevanter Herzinsuffizienz mit reduzierter linksventrikulärer Auswurffraktion o. symptomatischen Herzrhythmusstörungen in d. Anamnese. Mangels Daten bei eingeschränkter Leberfunktion u. bei Patienten mit Transaminasen-Anstieg größer 5fach des oberen Normwertes. Keine gleichzeitige Anwendung von anderen Arzneimitteln, die das QT-Intervall verlängern! **Warnhinweise:** Vorsicht bei Patienten mit ZNS-Erkrankungen, die zu Krampfanfällen prädisponieren o. bei denen die Krampfschwelle herabgesetzt ist. Bei einer Beeinträchtigung des Sehens o. Sehorgans ist d. Augenarzt umgehend zu konsultieren. Sehnenentzündungen u. Rupturen können unter d. Behandlung mit Chinolonen auftreten, insb. bei älteren Patienten o. bei gleichzeitiger Gabe von Kortikosteroiden. Vorsicht bei Patienten mit Begleitmedikation, die den Kaliumspiegel vermindern kann sowie bei Patienten mit Prädisposition zu Arrhythmien wie z. B. akuter Myokardischämie. Eine QT-Verlängerung kann d. Risiko kardialer Arrhythmien einschl. Torsade de pointes steigern. Da das Ausmaß der QT-Verlängerung mit der Infusionsgeschwindigkeit und der Plasmakonzentration ansteigen kann, Infusionsdauer (60 Minuten) nicht unter- und empf. Dosis nicht überschreiten. Patienten vor allem bei der ersten Infusion sorgfältig überwachen. Bei weniger schweren Infektionen Behandlungsnutzen gegenüber den möglichen Risiken abwägen. Bei Anzeichen kardialer Arrhythmie die Behandlung abbrechen u. EKG ableiten. Bei entspr. Anzeichen Leberfunktion überprüfen. Pseudomembranöse Kolitis ist unter d. Anwendung von Breitspektrum-Antibiotika beschrieben. Patienten mit Glucose-6-phosphat-Dehydrogenase-Mangel (auch in d. Familienanamnese) können unter Behandlung mit Chinolonen hämolytische Reaktionen entwickeln. Bei Chinolonen generell mögliche Photosensitivitätsreaktionen wurden bei Moxifloxacin nicht beobachtet (trotzdem übermäßiges/starkes Sonnenlicht vermeiden). Überempfindlichkeit und allerg. Reaktionen können schon nach der ersten Anwendung von Chinolonen auftreten, in sehr seltenen Fällen anaphylakt. Reaktionen bis hin zum lebensbedrohlichen Schock. In diesen Fällen ist Moxifloxacin sofort abzusetzen und eine geeignete Behandlung (z. B. Schocktherapie) ist einzuleiten. Wegen des Lactose-Gehalts keine Anwendung von Avalox® Filmtabletten bei Patienten mit Galactoseintoleranz, Lactasemangel oder Glucose-Galactose-Malabsorption. Avalox® Infusionslösung enthält 787 mg (ca. 34 mmol) Natrium pro Dosis. **Nebenwirkungen:** Bauchschmerzen, Kopfschmerzen, Reaktionen an der Einstichstelle (z. B. Ödeme, Überempfindlichkeit, Entzündung, Schmerz und in weniger als 1% Phlebitis); Benommenheit, Übelkeit, Durchfall, Erbrechen, Dyspepsie; QT-Streckenverlängerungen (bei gleichzeitig bestehender Hypokaliämie); Geschmacksstörungen; veränderte Leberfunktionstests. Asthenie, Schmerzen, Rückenschmerzen, allgemeines Unwohlsein, Schmerzen im Brustbereich; allergische Reaktionen, Schmerzen in den Beinen; Schläfrigkeit, Schwindel, Nervosität, Schläfrigkeit, Angstzustände, Tremor, Parästhesien, Verwirrtheit, Depression; Mundtrockenheit, Übelkeit mit Erbrechen, Blähungen, Verstopfung, orale Candidose, Anorexie, Stomatitis, Glossitis; Tachykardie, periphere Ödeme, Bluthochdruck, Palpitationen, Vorhofflimmern, Angina pectoris, QT-Streckenverlängerungen bei Normokaliämie; Dyspnoe; Arthralgie, Myalgie; Rash (flüchtiges Exanthem), Pruritus, Schwitzen, Urtikaria; Amblyopie, Vaginalcandidose, Vaginitis; gamma GT-Anstieg, Amylaseanstieg, Leukopenie; Prothrombinabfall/INR-Anstieg, Eosinophilie, Thrombozythämie, Thrombopenie, Anämie. Halluzination, Depersonalisation, Koordinationsstörungen, Unruhe, Schlafstörungen, anormale Träume, Krämpfe; Vasodilatation, Hypotension, Synkope; Tendinitis; Hauttrockenheit; Tinnitus, Sehstörungen aufgrund von ZNS-Reaktionen (z. B. Benommenheit oder Verwirrtheit). Parosmie (einschließlich Störungen des Geruchsvermögens, Abnahme des Geruchsvermögens, in seltenen Fällen Verlust des Geruchs- und/oder Geschmacksvermögens); Hyperglykämie, Hyperlipidämie, Prothrombinanstieg/INR-Abfall, Ikterus (vorwiegend cholestat.), LDH-Anstieg (in Verbindung mit veränderter Leberfunktion), Anstieg von Kreatinin oder Harnstoff. Anaphylakt. Reaktionen (bis zum Schock); Angioödem (inkl. Larynxödem); psychotische Reaktionen; pseudomembranöse Kolitis, Hepatitis (vorwiegend cholestat.), ventrikuläre Arrhythmie, Torsade de pointes, Herzstillstand; Sehnenruptur, Stevens-Johnson-Syndrom. Bei anderen Fluorochinolonen in Einzelfällen beobachtet und deshalb auch bei Avalox möglich: vorübergehender Verlust des Sehvermögens, Gleichgewichtsstörungen einschließlich Ataxie, Hypernatriämie, Hyperkalzämie, Neutropenie, Hämolyse. Verschreibungspflichtig. Stand: D/3.1; (April 2004) Bayer Vital GmbH, 51368 Leverkusen

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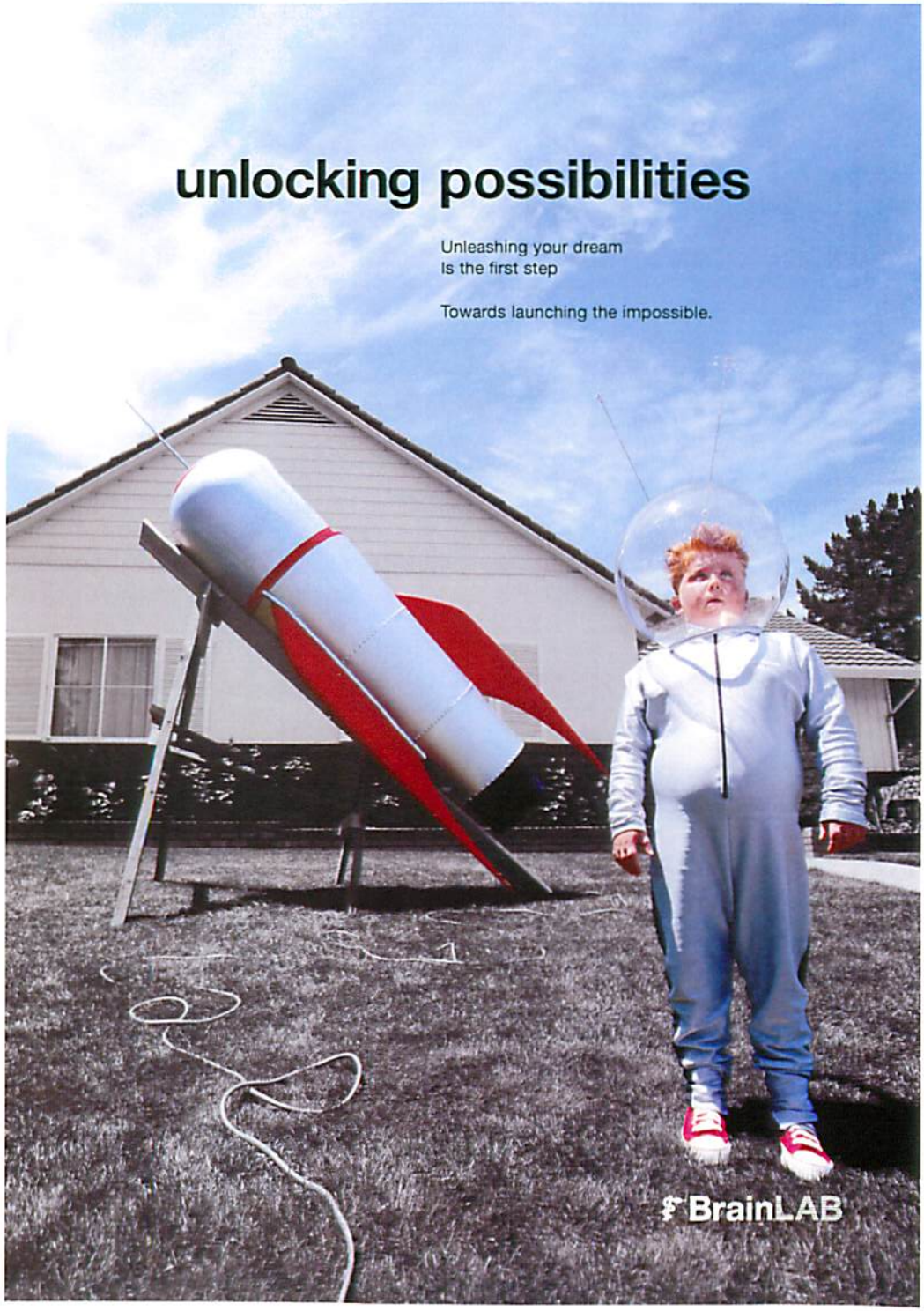
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