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OF MEDICINE AND PHARMACY

DOCTORAL SCHOOL NEUROSCIENCE

PROGRAM

2017-2018 | SECTION 5

15 FEBRUARY, 2018
"MULTIMEDIA" AUDITORIUM, "IULIU HATIEGANU" UMF CLUJ-NAPOCA
8 VICTOR BABES STREET | CLUJ-NAPOCA | ROMANIA
I. GOINA AUDITORIUM, 23 GHEORGHE MARINESCU STREET | CLUJ-NAPOCA | ROMANIA

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COURSE PROGRAM

COURSE PROGRAM

FEBRUARY 15TH, 2018

"MULTIMEDIA" AUDITORIUM, "IULIU HATIEGANU" UMF CLUJ-NAPOCA
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09:50 – 10:00	Welcome Address
10:00 – 10:40	Wolf Dieter Heiss / Germany Pathophysiology of Ischemic Stroke
10:40 – 11:20	Wolf Dieter Heiss / Germany Imaging in Acute Ischemic Stroke
11:20 – 11:50	Coffee Break
11:50 – 12:30	Wolf Dieter Heiss / Germany Imaging for Prediction of Recovery and Outcome after Stroke
12:30 – 13:10	Wolf Dieter Heiss / Germany Treatment of Acute Ischemic Stroke
13:10 – 16:00	Session Break

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16:00 – 16:40	Michael Brainin / Austria Post-stroke cognitive decline: Intervention trials for prevention and treatment
16:40 – 17:20	Michael Brainin / Austria Functional anatomy of the brain
17:20 – 17:50	Coffee Break
17:50 – 18:30	Michael Brainin / Austria Efficacy of stroke units
18:30 – 19:10	Michael Brainin / Austria Clinical Trials in Stroke Rehabilitation

INTERNATIONAL GUEST LECTURERS

MICHAEL BRAININ
AUSTRIA

Professor Brainin is full Professor of Clinical Neurology at the Danube University in Krems, Austria, and Director and Chair of the Department of Clinical Neurosciences and Prevention. He also is Chair and Professor at the Department of Neurology at the Karl Landsteiner University Hospital Tulln, Austria, an 86 bed neurological tertiary service hospital.

His research focus is on cerebrovascular diseases including acute therapy, recovery and cognition. He has published more than 251 peer-reviewed articles, 175 of them Pub med listed, mostly on stroke treatment and rehabilitation. His h-index is 32, he has 4040 citations. He has been an invited lecturer and chairperson to more than 1000 international conferences. He has published and edited several books, among them the Textbook of Stroke Medicine 2015 (with WD Heiss, Cambridge Univ. Press 2nd edition 2015). He was PI and Co-PI as well as contributor to many international stroke trials.

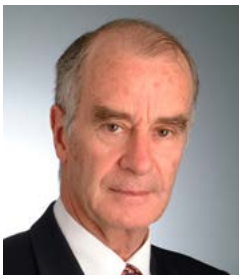
From 2012-2014 he was President of the European Stroke Organization (ESO), from 2008-2014 he was Treasurer and since 2014 Vice-President of the World Stroke Organization (WSO). In 2015 he was elected President Elect of the World Stroke Organisation due to take office in 2018.

Until 2008 he was chair of the Stroke Scientist Panel of the EFNS. He was appointed chair of the Scientific Committee of the European Federation of Neurological Societies (EFNS) from 2008-2014 during which time he was responsible for the production and editing of neurological guidelines. He was a member of several EFNS Programme Committees and also for the first congresses of the European Academy of Neurology in 2014 and 2015. In 2014 he was elected as individual full Board member of the EAN. For the EAN, he currently serves as member in the Scientific Committee. For the last 2 years he has served as co-chair of the Scientific Subspecialty Panel General neurology together with Jean Schoenen.

He is chairman of the WSO Education Committee (2008-) for which he has co-directed teaching programmes in many regions of the world. He is editor-in-chief of the World Stroke Academy. He directs several postgraduate teaching programmes at his university, among them the WSO supported European Master's Programme in Stroke Medicine.

He serves as Associate Editor for the European Journal of Neurology, Senior Consulting Editor and Section Editor (Recovery and Rehabilitation) for 'Stroke' and Section Editor (Education) for the "International Journal of Stroke'. Professor Brainin also serves on a number of Editorial Boards, among them Neuroepidemiology, and the Journal of Neurological Sciences.

Professor Brainin is a Fellow of the ESO and International Fellow of the American Stroke Association. He received several awards, such as the Marinescu Award 2015 from the Romanian Society of Neurology and Honorary Doctorates from Hanoi University, Vietnam, and from the University of Cluj, Romania, an honorary professorship from Zhengzhou University, as well as honorary memberships of the French Neurological Society, Hungarian Stroke Society and Indian Stroke Society.



WOLF DIETER HEISS

GERMANY

Wolf-Dieter Heiss graduated in medicine from the University of Vienna, Austria, in 1965. He achieved his training in neurology, neurophysiology, psychiatry and nuclear medicine at the University hospital in Vienna and spent research fellowships at the MIT, Cambridge, USA, the Physiological Institute in Stockholm, Sweden, the Department of Physiology of SUNY, Buffalo, NY and the Department of Neurology of the University of Minnessota, Minneapolis, USA. 1976 he was appointed associate professor at the Department of Neurology of the University of Vienna. In 1978 he became director of the Center for Cerebrovascular Research of the Max Planck Institute for Brain Research and of the Department of Neurology of the City Hospital Cologne-Merheim, Germany. 1981 he was appointed as director at the Max Planck Institute for Neurological Research. 1985 – 2005 he was professor of neurology and chairman of the Department of Neurology of the University of Cologne and director of the Department of General Neurology at the MPI in Cologne. He was president of the International Stroke Society 1992-96, was on the board of directors of the Society for Cerebral Blood Flow and Metabolism, deputy editor of the Journal of Cerebral Blood Flow and Metabolism and at present is associate editor of the Journal of Nuclear Medicine and section editor of Stroke. He was chairman of the program committee of the European Federation of Neurological Societies (EFNS) 1998 - 2001 and was president of the EFNS 2001 – 2005. Since 2005 he is Visiting Professor at the Danube Univerity in Krems, Austria, since 2009 Adjunct Professor at the McGill University in Montreal, Canada, and since 2013 Associate Professor, Dept of Neurosciences, Univ. Iuliu Hatieganu, Cluj, Romania. In December 2014 he received Dr. honoris causa of Univ. Iuliu Hategianu, Cluj, Romania.

DAFIN F. MUREȘANU
ROMANIA

Professor of Neurology, Senior Neurologist, Chairman of the Neurosciences Department, Faculty of Medicine, University of Medicine and Pharmacy "Iuliu Hatieganu" Cluj-Napoca, Past President of the Romanian Society of Neurology, President of the Society for the Study of Neuroprotection and Neuroplasticity (SSNN), member of the Academy of Medical Sciences, Romania, secretary of its Cluj Branch. He is member of 16 scientific international societies (being member of the American Neurological Association (ANA) - Fellow of ANA (FANA) since 2012) and 10 national ones, being part of the executive board of most of these societies. Professor Dafin F. Muresanu is a specialist in Leadership and Management of Research and Health Care Systems (specialization in Management and Leadership, Arthur Anderson Institute, Illinois, USA, 1998 and several international courses and training stages in Neurology, research, management and leadership). Professor Dafin F. Muresanu is coordinator in international educational programs of European Master (i.e. European Master in Stroke Medicine, University of Krems), organizer and co-organizer of many educational projects: European and international schools and courses (International School of Neurology, European Stroke Organisation summer School, Danubian Neurological Society Teaching Courses, Seminars - Department of Neurosciences, European Teaching Courses on Neurorehabilitation) and scientific events: congresses, conferences, symposia (International Congresses of the Society for the Study of Neuroprotection and Neuroplasticity (SSNN), International Association of Neurorestoratology (IANR) & Global College for Neuroprotection and Neuroregeneration (GCNN) Conferences, Vascular Dementia Congresses (VaD), World Congresses on Controversies in Neurology (CONy), Danube Society Neurology Congresses, World Academy for Multidisciplinary Neurotraumatolgy (AMN) Congresses, Congresses of European Society for Clinical Neuropharmacology, European Congresses of Neurorehabilitation). His activity includes involvement in many national and international clinical studies and research projects, over 400 scientific participations as "invited speaker" in national and international scientific events, a significant portfolio of scientific articles (157 papers indexed on Web of Science-ISI, H-index: 17) as well as contributions in monographs and books published by prestigious international publishing houses. Prof. Dr. Dafin F. Muresanu has been honoured with: the University of Medicine and Pharmacy "Iuliu Hatieganu" Cluj-Napoca, Faculty of Medicine, "Iuliu Hatieganu Great Award 2016" for the best educational project in the last five years; the Academy of Romanian Scientists, "Carol Davila Award for Medical Sciences / 2011", for the contribution to the Neurosurgery book "Tratat de Neurochirurgie" (vol.2), Editura Medicala, Bucuresti, 2011; the Faculty of Medicine, University of Medicine and Pharmacy "Iuliu Hatieganu" Cluj-Napoca "Octavian Fodor Award" for the best scientific activity of the year 2010 and the 2009 Romanian Academy "Gheorghe Marinescu Award" for advanced contributions in Neuroprotection and Neuroplasticity.

ABSTRACTS

CLINICAL TRIALS IN STROKE REHABILITATION

MICHAEL BRAININ
Clinical Neurology Danube University Krems, Austria

Recently, promising areas for research have been outlined, which include: drug recovery for motor recovery, early mobilization, body-weight support treatmill training, robotics, virtual reality games, transcranial magnetic stimulation and multiple, combined interventions.

For clinical trials in these areas, issues of measurement, sample size, interventions, and outcomes have to be defined. Due to the multidimensionality and complexity of rehabilitation all these issues deserve separate consideration. Integration into social and community structures, life satisfaction, burden on relatives and caretakers, and psychic dimensions have to be taken into account.

In acute stroke predictors of outcome are comparatively simple and have been confirmed in many studies. Global scales have been preferred for better standardization and comparability across populations and countries. Mostly, for overall effect measures, 5-6 graded scales have been preferred, but are hampered by variability of definitions in middle categories. Scales with a larger number of items such as the Rivermead mobility Index are more precise but have larger interrater variabilities. The Barthel Index has been considered as being of limited value due to ceiling effects. On the other hand, simplified measures such as those used for gait training do not capture real life situations which include dual and multiple task issues.

For stroke rehabilitation trials the sample sizes used are small convenience samples and often result in beta measurement errors. Rehabilitation usually aims at smaller effect sizes and for this larger samples are needed, which represent a burden on budgets which are limited by grants or personnel costs. It occurs that larger sample sizes are planned at the cost of the intensity of the intervention which eludes the detection of group differences. For practical reasons and to avoid obvious critics, many rehabilitation trials are called proof-of-concept or pilot trials, but are usually not followed by larger phase 3 trials. Therefore, proper and extensive funding is crucial for the success of a trial. Usually, an effect size of 4-5 per hundred affords a sample size of 1.500. Smaller effect sizes result in much larger sample sizes needed and might afford sizes of several 1.000patients such as for megatrials

Cognitive measures need to be included in many neurorehabilitation trials. For this, "Vascular Cognitive Impairment Harmonization Standards" have been proposed with a 5 minute and 30 minute investigation block. Also for stroke rehabilitation trials surrogate outcomes are important and need to be established. Hardly any accepted standards exist to date. While for risk factor modification the intima-media thickness seems to a cheap and reliable surrogate outcome, other outcomes including from those from neuroimaging, voxel-based morphometry based measurements, preservation of networking characteristics in fibre tracking imaging, as well as from positron tomography imaging are currently under investigation.

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EFFICACY OF STROKE UNITS

MICHAEL BRAININ
Clinical Neurology Danube University Krems, Austria

Organised stroke unit care is a form of care provided in hospital by nurses, doctors and therapists who specialise in looking after stroke patients and work as a co-ordinated team. An updated systematic review has confirmed significant reductions in death (3% absolute reduction), dependency (5% increase in independent survivors) and the need for institutional care (2% reduction) for patients treated in a stroke unit, compared with those treated in general wards. All types of patients, irrespective of gender, age, stroke subtype and stroke severity, appear to benefit from treatment in stroke units. These results have been confirmed in large observational studies of routine practice. Stroke units may also improve patients' quality of life, and improvements in outcome may persist for several years. Of available therapies in the acute phase of stroke (antiplatelet therapy, intravenous thrombolysis, stroke unit care), stroke unit care has the overall largest benefit because this principle of care may potentially be applied to all patients with acute stroke.

The core components of stroke unit care include

- Rapid medical assessment and diagnosis, and early assessment of nursing and therapy needs
- early management, consisting of early mobilization, prevention of complications, and treatment of hypoxia, hyperglycaemia, pyrexia and dehydration
- ongoing rehabilitation, involving coordinated multidisciplinary team care, and early assessment of needs after discharge.

Making an early diagnosis of stroke is crucial because a time-dependent deterioration occurs that is caused by oxygen depletion in the neural tissue that shows ongoing compromise of blood-flow. Without intervention this compromised area of the brain will develop into an infarct and cannot be rescued. This critical time, which enables us to perform recanalisation and reperfusion therapy is called therapeutic time window. If one quantifies the time factor of ischemia it has been estimated that up to two million neurons will be lost per minute which amounts to more than 30.000 neurons per second. Thus, it is important to recognize stroke as an emergency. Persons with stroke should be hospitalized and treated as soon as possible. In many countries there is a recommended chain of recovery which includes firstly the recognition of stroke, then the reaction towards stroke, then the response, the reveal and the treatment.

In some regions of the world these transport systems are well developed and the ambulance personnel regularly receives special training. Once the patient arrives in the emergency department it should be clear that an urgent triage and a priority code should be assigned to a stroke patient. Priority includes the setting up of an IV line, measuring blood glucose, performing routine biochemistry including blood count and performing standard ECG. Trained medical personal should perform an accurate clinical diagnosis and exclude mimics. Under ideal circumstances, the stroke team should be notified before the arrival of the patient and urgent clarification of the diagnosis preferably by usage of brain imaging as soon as possible should be thought for.

Thrombolytic therapy should be used by personnel trained in its use in a centre equipped to investigate and monitor patients appropriately. Currently thrombolysis is only approved for treatment within 4.5 hours of symptom onset. Thrombolysis requires admission of stroke to hospital and it cannot easily be given in small local hospitals. More recently, endovascular thrombectomy has become standard treatment for large thromboses in the M1 or 2 segment of the ACM which usually causes severe strokes with NIHSS values of 15 or more. This therapy can only be applied within 6 hours of onset and must be performed in specialized comprehensive stroke centers.

In the acute phase, aspirin is associated with a very significant reduction in acute ischemic strokes, as well as deaths (of any cause) and the combined end-point of death and further strokes. There is no significant access of intracerebral hemorrhages. Subgroup analyses showed that aspirin was beneficial in all types of ischemic strokes irrespective of age and gender. For every 1000 patients treated aspirin treatment avoids 9 deaths or stroke in the acute phase, 12 death and dependency, and an extra 10 patients make a complete recovery. Consequently, prompt treatment with aspirin should be considered for almost all patients presenting with suspected acute ischemic stroke.

Strategies to prevent further strokes should be initiated already when the patient is under early treatment for a first stroke. All patients with stroke (ischemic, hemorrhagic, and stroke of unknown cause) will benefit from modification of life style changes, in particular cessation of smoking, and blood pressure reduction with a diuretic and an ACE-inhibitor. Blood pressure reduction should not be started until after the acute phase.

Patients with ischemic stroke benefit from long-term use of antiplatelet therapy as well as from a statin if total cholesterol is >3.5 mmol/liter.

The structure and process quality of stroke units include that there is a seamless and constant observation of vital parameters including blood pressure, heart rate, temperature, breathing and other parameters. This adds to the direct observation of the patient by trained personnel to notice early changes in the state of consciousness, to recognize epileptic fits and extracerebral causes of clinical deterioration.

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FUNCTIONAL ANATOMY OF THE BRAIN

MICHAEL BRAININ
Clinical Neurology Danube University Krems, Austria

Localization of function within the brain was the starting point for clinical neurology. Only with Brodman the cartography of the cerebral cortex based on clinical observation and experiments had a lasting effect and was accepted as the basis of localization of function of the cortex. Controversies among great minds of neurology took place and had to wait for pathological confirmation which often took years. The dichotomy of localization and function was united in a model by Luria who laid the foundations of modern neuroplasticity. Neuroimaging enabled neurologists and neurosurgeons to localize function much more easily and speculations about functional models could be put to a test. Tailarach and his school in Marseille founded stereotactic localisation and laid this down in his famous atlas which allowed the exact location pinpointed in the depth of the hemispheres and enabled comparability among humans. Later on, based on modern imaging, brain atlases were developed to guide the clinician and researcher on the transversal, coronary, or sagittal cuts of CT and MRI images. Among the most notable ones was the CT/MRI Atlas of Hanna and Antonio Damasio developed as a guide for vessel anatomy and cortical Brodman areas, This is especially helpful for analysis of small groups of patients who have similar lesions or similar clinical deficits and can used in a semiquantitative way. Finally, Marsel Mesulam from Boston proposed a functional model of the human cortex which allows interpretation of function in health and disease alike. This combined usefulness allows the interpretation of cortical syndromes as disconnection disturbances and explains most neuropsychological syndromes on the basis of disconnected localisation of function, either intra- or interhemispheric. New methods of imaging such as fibre tract imaging or functional MRI confirm these models and visualize such disconnections. Several examples will be given, including the neuroanatomical basis of problem solving, the working mind of a calculating prodigy, or the neural basis of frontal lobe dysfunctions.

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POST-STROKE COGNITIVE DECLINE: INTERVENTION TRIALS FOR PREVENTION AND TREATMENT

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Clinical Neurology Danube University Krems, Austria

Previous randomized trials aiming at promoting recovery after stroke such as with levodopa, natural biologicals (Cerebrolysin) or SSRI's have been successful in showing improvement of motor recovery. But currently no established treatment exists for the preservation or restoration of cognitive status following stroke. Given the high frequency of delayed onset of cognitive deterioration following stroke it is surprising that large studies have yet to be performed. Single or combined drug interventions tested up to now were based on secondary outcome analyses and included antihypertensive drugs which showed only a modest effect on cognition in general and no consistent effect was shown for lipid lowering drugs. Combination of antiplatelet drugs have been tested in the SPS3 trial but showed no effect on cognitive outcomes. Life-style interventions include studies of a Mediterranean diet with extra virgin olive oil and nuts but while stroke occurrence can be reduced, no data on post-stroke cognition exist. The same applies for physical exercise programs which show good effects on physical fitness.

Ongoing registered stroke testing either drug and/or lifestyle interventions all are planned either for small sample sizes and /or a complex endpoint or combination of endpoints that are not likely to produce practice-changing results.

Multi-domain intervention studies are much more likely to be effective on cognition because they perform multiple risk factor management with lifestyle adaptation including diet changes with increase of drug compliance and adherence. Intensifying these interventions and to monitor them is crucial. The first comprehensive multi-domain intervention trial (ASPIS) has recently been terminated. The primary endpoint was a significant change of the z-score of 5 neuropsychologically assessed cognitive domains. While the overall result was neutral, a signal for change of dysexecutive function was seen and follow-up studies might have to consider this finding. In the future, there is a need for including cognitive outcome measurements in all trials targeting the brain, to consider larger sample sizes, to harmonize assessment strategies, to focus on a high risk population, and to include biomarkers and imaging data for confirmatory analyses. Overall, it is crucial to aim for intervention intensities that create significant group differences.

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IMAGING IN ACUTE ISCHEMIC STROKE

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Imaging studies are used to exclude hemorrhage in the acute stroke patient, to assess the degree of brain injury, and to identify the vascular lesion responsible for the ischemic deficit. Some advanced CT and MRI technologies as well as PETare able to distinguish between brain tissue that is irreversibly infarcted and that which is potentially salvageable, thereby allowing better selection of patients likely to benefit from therapy.

CT has the advantage of being available 24 hours a day and is the gold standard for hemorrhage.
Hemorrhage on MR images can be quite confusing. On CT 60% of infarcts are seen within 3-6 hrs and virtually all are seen in 24 hours. The overall sensitivity of CT to diagnose stroke is 64% and the specificity is 85%. Hypoattenuation on CT is highly specific for irreversible ischemic brain damage if it is detected within first 6 hours (1). Patients who present with symptoms of stroke and who demonstrate hypodensity on CT within first six hours were proven to have larger infarct volumes, more severe symptoms, less favorable clinical courses and they even have a higher risk of hemorrhage. Obscuration of the lentiform nucleus, also called blurred basal ganglia, and hypodensity and swelling of the insular cortex are also important signs of infarction. A dense MCA sign is a result of thrombus or embolus in the MCA. 15% of MCA infarcts are initially hemorrhagic. Hemorrhage is most easily detected with CT, but it can also be visualized with gradient echo MR-sequences. With CT and MR-diffusion we can get a good impression of the area that is infarcted, but we cannot preclude a large ischemic penumbra (tissue at risk).

MRI: High signal on conventional MR-sequences is comparable to hypodensity on CT.
It is the result of irreversible injury with cell death. So hyperintensity means BAD news: dead brain. On PD/T2WI and FLAIR infarction is seen as high SI. These sequences detect 80% of infarctions before 24 hours. They may be negative up to 2-4 hours post-ictus! DWI is the most sensitive sequence for stroke imaging. DWI is sensitive to restriction of Brownian motion of extracellular water due to imbalance caused by cytotoxic edema. Perfusion with MR is comparable to perfusion CT. The area with abnormal perfusion can be dead tissue or tissue at risk. Combining the diffusion and perfusion images helps us to define the tissue at risk, i.e. the penumbra.

Positron emission tomography (PET) is still the only method allowing quantitative determination of various physiologic variables in the brain and was applied extensively for studies in patients with acute, subacute or chronic stages of ischemic stroke. The quantitative measurement of CBF, CMRO2, OEF and CBV permitted the independent assessment of perfusion and energy metabolism, and demonstrated the uncoupling of these usually closely related variables. These studies provided data on flow and metabolic variables predicting final infarction on late CTs (rCBF less than 12 ml/100g/min, CMRO2 less than 65 µmol/100g/min). Relatively preserved CMRO2 indicated maintained neuronal function in regions with severely reduced CBF; this pattern was coined "misery perfusion" and served as a definition for the penumbra, which is characterized by increased oxygen extraction fraction (up to more than 80 % from the normal 40 – 50 %). Late CT or MRI often showed these regions as morphologically intact. PET thus permits the differentiation of various tissue compartments within an ischemic territory: Irreversible damage by decreased flow and oxygen consumption below critical thresholds; misery perfusion, i.e. penumbra, by decreased flow, but preserved oxygen utilization above a critical threshold, expressed by increased OEF; luxury perfusion by flow increased above the metabolic demand; anaerobic glycolysis by a change in the ratio between glucose metabolism and oxygen utilization. However, PET has severe disadvantages limiting its routine application in patients with stroke: it is a complex methodology, requires multitracer application, and quantitative analysis necessitates arterial blood sampling. Although PET remains the imaging gold standard for identification of the penumbra in stroke patients, MR studies using diffusion and perfusion-weighted imaging might provide a differentiation between the core and the penumbra: the early diffusion weighted imaging (DWI) lesion might define the ischemic core and adjacent critically hypoperfused tissue might be identified with perfusion-weighted imaging (PWI). However, this surrogate definition of the penumbra has several uncertainties: the mismatch volume in PW / DWI as conventionally calculated does not reliably reflect misery perfusion, i.e. the penumbra as defined by PET.

PATHOPHYSIOLOGY OF ISCHEMIC STROKE

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The burden of cerebrovascular disease (CVD) is extremely high: in 2000 there were 15.3 million strokes worldwide, 5.5 million resulted in death (WHO 2008). But CVD accounts not only for 10 % of all deaths; it is the leading cause of disability in patients surviving the insult The energy demands of the nervous tissue are very high and therefore sufficient blood supply to the brain must be maintained consistently. A normal adult male's brain containing approx. 130 billion neurons (21.5 billion in the neocortex) (Pakkenberg and Gundersen 1997) comprises only 2 % of total body mass, yet consumes at rest approximately 20 % of the body's total basal oxygen consumption supplied by 16 % of the cardiac blood output. The brain's oxygen consumption is almost entirely for the oxidative metabolism of glucose, which in normal physiological conditions is the almost exclusive substrate for the brain's energy metabolism.

Cerebrovascular diseases are caused by interruption or significant impairment of blood supply to the brain, which leads to a cascade of metabolic and molecular alterations resulting in functional disturbance and morphological damage. An understanding of the pathophysiological changes leading to functional impairment and irreversible tissue damage is important for the application of existing treatment and for the development of more effective therapeutic strategies. For therapeutic interventions in acute ischemic stroke the concept of the penumbra, i.e. of tissue at reduced perfusion with a disturbed function but preserved morphological integrity, and of the time-dependent progression of irreversible tissue damage, play a central role. Regional flow changes below critical values trigger a cascade of physiologic and biochemical alterations (breakdown of energy metabolism, ATP-depletion, membrane depolarization, glutamate liberation, influx of sodium and calcium into the cells, outflux of potassium, spreading depression like depolarizations, liberation of cytokines, etc) and later-on cause cytotoxix and vasogenic edema and neuroinflammtion.

The pathophysiological changes were intensively investigated in animal models of cerebral ischemia, but many of those are not reflecting the pathological changes occuring in human stroke. For translational research of ischemic stroke pathophysiological changes can be assessed by positron emission tomography (PET), which permits to measure regionally various physiologic parameters and to image the distribution of molecular markers. PET was essential in the transfer of the concept of the penumbra, i.e. tissue with perfusion below the functional threshold, but above the threshold for preservation of morphology, to clinical stroke and thereby had a great impact on developing treatment strategies. Radioligands for receptors can be applied as early markers of irreversible neuronal damage and thereby can predict the size of the final infarcts, which is also important for decisions of invasive therapy in large ("malignant") infarction. With PET investigations the reserve capacity of blood supply to the brain can be tested in obstructive arteriosclerosis of supplying arteries. The effect of a stroke on surrounding and contralateral primarily not-affected tissue regions of the functional network can be investigated. Despite clinical application of PET is limited it has a great impact on research in cerebrovascular diseases.

IMAGING FOR PREDICTION OF RECOVERY AND OUTCOME AFTER STROKE

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Neuroimaging modalities may help to assess functional outcome and to predict the efficacy of rehabilitation in individual patients additionally to functional assessment scales such as NIHSS and others.

CT: The most widely used imaging procedure in acute stroke is CT, especially for differentiation between hemorrhagic and ischemic stroke, for localization of the lesion and for decision making regarding administration of potentially risky stroke therapies as thrombolysis. ASPECTS (the Alberta Stroke Program Early Computed Tomography Score) is a measure to quantify ischemic changes on CT within the territory of the middle cerebral artery (MCA) and can help select patients for acute intravascular treatment.

MRI: With diffusion-weighted imaging (DWI), the size of the lesion can be outlined early and DWI lesion volume significantly increased the power of prediction models. Diffusion tensor imaging (DTI) measures may also be used to predict outcome. The connectivity in networks as assessed by DTI is more important for outcome and recovery than the extent of the primary structural lesion.

Assessment of brain blood supply and cerebral perfusion.

Inclusion of information from CT angiography contributed significantly more to outcome prediction than the ASPECTS score. Evidence of large vessel occlusion is crucial for improving outcome by early endovascular interventions. The final size of an infarct is also influenced by the extent and quality of collateral circulation to the affected brain area. The presence of robust collateral flow is best visualized by conventional angiography, but CT angiography as a non-invasive alternative has better spatial resolution than transcranial Doppler or MR angiography and can depict leptomeningeal collaterals.

The visualization of disturbed interaction in functional networks and of their reorganization in the recovery after focal brain damage is the domain of functional imaging modalities such as PET and fMRI. PET: Mapping of neuronal activity in the brain can be primarily achieved by quantitation of the regional cerebral metabolic rate for glucose (CMRGlc). Quantitative imaging of cerebral blood flow (CBF) is based on the principle of diffusible tracer exchange, using 15O-labeled water. PET detects and, if required, can quantify changes in CBF and CMRGlc accompanying different activation states of brain tissue. The regional values of CBF or CMRGlc represent the brain activity due to a specific state, task or stimulus in comparison with the resting condition, and color-coded maps can be analyzed or correlated to morphological images.

fMRI measures signals that depend on the differential magnetic properties of oxygenated and deoxygenated hemoglobin, termed the blood-oxygen-level-dependent (BOLD) signal, which gives an estimate of changes in oxygen availability. The amount of deoxyhemoglobin in small blood vessels depends on the flow of well-oxygenated arterial blood (CBF), on the outflow of O2 to the tissue (CMRO2) and on the cerebral blood volume (CBV). fMRI images map changes in brain function and can be superimposed on the anatomical image.

Motor and somatosensory deficits: In most fMRI or PET studies involving active or passive movements, a widespread network of neurons was activated in both hemispheres. During recovery from hemiparesis, a dynamic bihemispheric reorganization of motor networks takes place. Ipsilateral cortical recruitment seems to be a compensatory cortical process related to the lesion of the contralateral primary motor cortex. The unaffected hemisphere actually inhibits the generation of a voluntary movement by the paretic hand. This effect of transcallosal inhibition can be reduced by repetitive transcranial magnetic stimulation (rTMS).

Post-stroke aphasia: Studies of glucose metabolism in aphasia after stroke have shown metabolic disturbances in the ipsilateral hemisphere caused by the lesion and contralateral hemisphere caused by functional deactivation (diaschisis). Patients with an eventual good recovery predominantly activated structures in the ipsilateral hemisphere. Combination of repetitive transcranial magnetic stimulation (rTMS) with activated imaging: Activation studies in the course of recovery

of post-stroke aphasia suggest various mechanisms for the compensation of the lesion within the functional network: restoration of the original activation pattern, activation of areas around the lesion (intrahemispheric compensation) and reduction of transcallosal inhibition causing activation of contralateral homotopic areas. rTMS is a non-invasive procedure to create electric currents in discrete brain areas which, depending on frequency, intensity and duration, can lead to transient increases (with higher frequencies) and decreases (with lower frequencies) in excitability of the affected cortex. The role of activation in the right hemisphere for residual language performance can be investigated by combining rTMS with functional imaging, e.g. PET. Counteraction by rTMS of contra-lateral active areas might open a new therapeutic strategy for post-stroke aphasia.

TREATMENT OF ACUTE ISCHEMIC STROKE

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Ischemic stroke is the second most common cause of death worldwide and the third leading cause of the loss of disability-adjusted life years; however, treatment remains insufficient and is only successful during the first hours after the attack if reperfusion of the ischemic territory can be achieved. Thrombolysis resulting from the intravenous administration of recombinant tissue plasminogen activator (rt-PA) within 4.5 h significantly reduces the incidence of death or dependency at 3 to 6 months, but the benefit of its administration ceases between 4.5 and 6 h after the ictus.3 Attempts to recanalize occluded vessels after this time window by intra-arterial rt-PA or mechanical thrombectomy enhance reperfusion and have recently been shown to improve clinical outcome in carefully selected patients. However, the number of patients who may benefit from these reperfusion therapies is small and probably totals less than 20% of all stroke victims, even for those treated at specialized centers.

Therefore, many therapeutic strategies have been developed targeting the pathophysiological cascade that starts with ischemia and ultimately leads to irreversible tissue damage. Despite beneficial results obtained in the prevention of the development of infarcts and patient outcome following experimental ischemia, neuroprotective drugs have not shown efficacy in clinical trials. This failure to translate results from experimental studies to clinical application might be due in part to the use of inappropriate animal model and also to the design of human trials, which often do not consider the limited time windows of targeted steps in the pathophysiological cascade or the complexity of the biochemical and molecular mechanisms leading to ischemic brain damage. As a consequence, treatments directed at correcting one biochemical or molecular step in the pathophysiological cascade of ischemic cell damage have not been successful in stroke, warranting the testing of a multi-targeted therapy that includes compounds with effects on several of the associated pathophysiologic events. One of these multimodal compounds is Cerebrolysin, which has been shown to have neuroprotective properties and to exhibit neurotrophic activity. In animal models and several clinical studies Cerebrolysin had a beneficial effect on function and global outcome in early rehabilitation patients after stroke.