Special Report

Third European Stroke Science Workshop

Martin Dichgans, MD; Anna M. Planas, PhD; Geert Jan Biessels, MD; Bart van der Worp, MD; Cathie Sudlow, MD; Bo Norrving, MD; Kennedy Lees, MD; Heinrich P. Mattle, MD

Abstract—Lake Eibsee, Garmisch-Partenkirchen, November 19 to 21, 2015: The European Stroke Organization convened >120 stroke experts from 27 countries to discuss latest results and hot topics in clinical, translational, and basic stroke research. Since its inception in 2011, the European Stroke Science Workshop has become a cornerstone of European Stroke Organization’s academic activities and major highlight for researchers in the field. Participants include stroke researchers at all career stages who convene for plenary lectures and discussions, thus facilitating crosstalk among researchers from different fields. As in previous years, the workshop was organized into 7 scientific sessions each focusing on a major research topic. All sessions started with a keynote lecture that provided an overview on current developments and set the scene for the following presentations. The latter were short focused talks on a timely topic and included the most recent findings, including unpublished data. A new element at this year’s meeting was a hot topic session in which speakers had to present a provocative concept or update sharply within 5 minutes. In the following, we summarize the key contents of the meeting. The program is provided in the online-only Data Supplement. (Stroke. 2016;47:e178-e186. DOI: 10.1161/STROKEAHA.116.013516.)

Key Words: cerebral small-vessel diseases ■ cognition ■ endovascular procedures ■ genetics ■ hemorrhage ■ stroke

Session I: Stroke Immunology (Anna Planas, Spain, and Ulrich Dirmagl, Germany)

Nancy Rothwell, United Kingdom, Addressed the Question Whether Stroke Immunology Is an Avenue for Treatment or a False Promise

Inflammatory and immune responses have both beneficial and detrimental effects on stroke incidence and outcome depending on their location, severity, duration, and nature. Interleukin-1 (IL-1) is an important inflammatory cytokine that is detrimental in experimental stroke. Therefore, it is timely to consider the potential clinical benefit of blocking IL-1, especially because the naturally occurring IL-1 receptor antagonist (IL-1Ra) has anti-inflammatory and beneficial properties in many human inflammatory diseases. Rothwell et al have shown that IL-1Ra markedly inhibits injury induced by cerebral ischemia in animal models. It is effective when administered peripherally, even some hours after the onset of ischemia, and protection is sustained as assessed by behavioral outcomes and magnetic resonance imaging (MRI). Blocking IL-1 using neutralizing antibodies, gene deletion or caspase-1 inhibition also reduces experimental ischemic brain damage. Furthermore, IL-1Ra is protective in animals with a range of comorbidities associated with clinical stroke, including diabetes mellitus, obesity, age, and infection, and hemorrhagic stroke. The mechanisms of IL-1 action in stroke as elucidated to date include effects in the periphery and in the brain. Hence, although it is known that IL-1Ra penetrates the brain in rodents and in subarachnoid hemorrhage patients, it may also have peripheral actions to reduce the systemic inflammatory response to stroke. The critical question now is whether the same or similar mechanisms operate in human stroke. IL-1Ra has proven safe and well tolerated in early clinical trials in acute ischemic stroke and subarachnoid hemorrhage. Phase 3 trials will have to demonstrate whether IL-1Ra is indeed effective.

Arthur Liesz, Germany, Presented Novel Experimental Data on Brain–Gut Microbiome Interaction in Stroke

Recent evidence suggests a role of the gut microbiota in autoimmune diseases by modulating immune homeostasis. However, its effect on poststroke adaptive immunity was previously unknown. Liesz et al demonstrated that stroke in mice causes microbiota dysbiosis, which in turn affects stroke...
outcome via immune-mediated mechanisms. Moreover, bacteriotherapy normalized brain lesion–induced dysbiosis and improved stroke outcome. These results support that the gut microbiome is a target of stroke-induced systemic alterations, as well as an effector with a substantial effect on stroke outcome. A recent study found dysbiosis of the gut microbiota in patients with stroke and transient ischemic attack, thus supporting that the findings of Liesz et al might be relevant to human stroke. However, some caution is warranted in translating specific aspects of dysbiosis between mice and humans.

Midori Yenari, United States, Addressed the Role of Triggering Receptor Expressed by Myeloid Cells 2 in Ischemic Stroke

Inflammation is thought to contribute negatively to acute stroke, but it also plays a role in recovery by clearing necrotic debris. Triggering receptor expressed by myeloid cells 2 is involved in the innate immune system, is expressed on microglia, and is a surface receptor involved in phagocytosis that promotes anti-inflammatory responses. Yenari et al found decreased phagocytosis and infarcted brain tissue resorption in triggering receptor expressed by myeloid cells 2–deficient mice compared with wild-type mice subjected to experimental stroke. Triggering receptor expressed by myeloid cells 2 further seems to be essential for neurological recovery in a stroke model.

Maria Grazia de Simoni, Italy, Reviewed the Role of the Lectin Pathway and the Complement System

The lectin complement pathway is involved in the progression of brain damage in stroke. A few studies highlighted 2 lectin complement pathway activation molecules, mannose-binding lectin and ficolin-3, as independent predictors of outcome after ischemic stroke in experimental animals and in patients. Mannose-binding lectin has multiple proinflammatory and toxic effects on brain endothelium, resulting in increased vascular damage, inflammation, and coagulation that might contribute to brain damage after stroke. Inhibition of mannose-binding lectin function in experimental stroke models leads to neuroprotection against ischemic brain injury with a wide therapeutic window.

Denis Vivien, France, Discussed Recent Advances in Molecular Imaging of Brain–Immune Interactions

Neuroinflammation is a hallmark and decisive player of central nervous system diseases. Adhesion molecules in activated endothelial cells, that is, vascular cell adhesion molecule 1, intercellular adhesion molecule 1, P-selectin, and E-selectin, can be visualized using MRI as biomarkers for neuroinflammation and brain–immune interactions. Vivien et al used microsized particles of iron oxide conjugated to monoclonal vascular cell adhesion molecule 1 antibodies for in vivo detection of cerebrovascular inflammation in mice. They demonstrated a sustained overexpression of vascular cell adhesion molecule 1 not only in the ischemic core but also in the periphery. Endothelial activation in potentially salvageable tissue suggests that noninvasive imaging of this inflammatory reaction could be useful to identify the penumbra.
Oliv Jansen, Germany, Reviewed Devices and Techniques for Mechanical Recanalization

Stent retrievers have been shown to be efficient in recanalizing large-vessel occlusion in patients with acute ischemic stroke. Recanalization rates with thrombolyis in cerebral infarction 2b/3 can be achieved in ≈75% of treated patients. Meanwhile, different new approaches have been described to further increase the recanalization rate, reduce the recanalization time, and reduce the rate of new emboli. Aspiration-alone techniques, protected stent retriever procedures, including the use of proximal balloon occlusion, and distal access catheters and new devices (ie, cover devices) have been developed and showed promising results in in vitro studies and first clinical observations. However, more valid clinical data are needed before these new or additional techniques for endovascular stroke treatment can be recommended for clinical use.

Jan Gralla, Switzerland, Addressed the Question “New Territory Infarcts—How to Assess, How to Prevent?”

Unlike intra-arterial thrombolysis, stent retriever thrombectomy carries the risk of thrombus dislodgement into proximal vessel segments and infarcts in new territories. In most cases, the patient deteriorates immediately because leptomeningeal collaterals from the previously unaffected territory to the initial infarct area are cutoff and infarct growth is accelerated.

Preinterventional imaging and continuous angiographic evaluation during intervention help to assess clot dislodgment and new territory infarcts. However, to date, there is no standardized reporting of peri-interventional and postinterventional complications of mechanical thrombectomy. The risk is estimated between 2% and 5% and depends on the occlusion pattern. Two complimentary techniques can prevent clot dislodgement: 1) proximal balloon occlusion of the ICA and flow reversal applying aspiration during thrombus retrieval and 2) local aspiration in direct proximity to the clot using an aspiration catheter navigated to the occlusion. Future studies should address protection techniques of mechanical thrombectomy and establish a standardized reporting of peri-interventional and postinterventional complications.

Alain Bonafé, France, Debated the Question “Conscious Sedation or General Anesthesia?”

Previous studies, a post hoc analysis of MR CLEAN study, and a recent meta-analysis suggest that general anesthesia may have a negative effect on outcome in patients undergoing endovascular therapy. The main drawbacks of general anesthesia are delay of the intervention and drug-induced hemodynamic changes. This carries the risk of aggravating ischemic and reperfusion injuries. On the other hand, general anesthesia reduces patient motion and procedural risks, and anesthetic drugs are potentially neuroprotective. Whether worse outcome after general anesthesia is related to patient selection and other factors, such as stroke severity, time to recanalization, blood glucose, blood pressure (BP) fluctuations, and location of vessel occlusion, remains to be determined. Several ongoing randomized single-center studies compare local and general anesthesia. However, multicenter trials would be preferable.

Session III: Small-Vessel Disease (Martin Lauritzen, Denmark, and Geert Jan Biessels, The Netherlands)

Oscar Benavente, Canada, Opened the Session With a Keynote Lecture on the Diagnosis and Treatment of Lacunar Stroke

The Secondary Prevention of Small Subcortical Strokes (SPS3) trial involved 3020 patients with recent symptomatic lacunar infarcts confirmed on MRI. In a 2-by-2 factorial design, patients were randomized to an antiplatelet intervention (ie, 75 mg of clopidogrel versus placebo, both combined with 325 mg of aspirin) and a BP intervention (ie, target levels for systolic BP <130 versus 130–149 mm Hg). The addition of clopidogrel to aspirin did not significantly reduce the risk of recurrent stroke but significantly increased the risk of bleeding and death. The results on BP lowering indicated that a systolic blood pressure target of <130 mm Hg might be beneficial for reducing the risk of recurrent stroke, but none of the interventions reduced cognitive deficits.

Hugues Chabriat, France, Reported on Predictors of Clinical Progression in CADASIL—A Pure Form of Small-Vessel Disease

In a large cohort study of 292 patients with CADASIL, gait disturbance, a positive history of stroke, and active smoking were found to predict incident stroke. Moderate or severe disability, smoking, male sex, and age predicted incident dementia. Looking at MRI, the number of lacunes and microbleeds predicted incident stroke and lower brain volume predicted progressive disability. When all factors were combined, gait disturbance, dementia, and brain MRI predicted progression toward moderate or severe disability, whereas active smoking, disability, and brain volume predicted incident dementia. These results were discussed with respect to findings obtained in sporadic small-vessel disease (SVD). Once brain injury and clinical severity have reached a certain level, clinical progression may accelerate.

Martin Lauritzen, Denmark, Addressed the Role of Pericytes in Regulating Cerebral Blood Flow

Brain microvessels, astrocytes, pericytes, and neurons together constitute the neurovascular unit, and the interplay between these cell types controls cerebral blood flow. Until recently, it was difficult to study the role of pericytes in this unit in vivo, but this has changed by the introduction of a mouse with pericytes expressing the fluorescent protein dsRed under control of the NG2 promoter and other types of transgenic mice. This permits the identification and examination of these cells in vivo by 2-photon microscopy. It seems that pericytes are specialized vascular smooth cells, with a variety of functions, including maintenance and regulation of the cerebral microcirculation and the blood–brain barrier. Recent data suggest that capillary pericytes increase brain–blood flow during rises in activity, whereas pericyte constriction decreases flow
after cerebral ischemia. Ongoing research aims to identify the mechanisms of blood flow and blood–brain barrier control by pericytes in health and disease.

Jeroen Hendrikse, The Netherlands, Presented Recent Developments in Ultrahigh Field MRI of Microvessel Structure and Function in Humans

Hendrikse showed that 7-T MRI can visualize small perforating arteries in the centrum semiovale and deep gray matter and even distinguish between arteries and veins. Furthermore, with high-resolution (0.2×0.2×0.2 mm) phase-contrast MRI and cardiac gating, blood flow velocity fluctuations and pulsatility of these small arteries can be assessed. These techniques may open the avenue for early noninvasive detection of functional changes of these arteries before brain tissue changes commence. We are therefore exploring which abnormalities of small-vessel structure and function can be detected in patients with SVD. This is one of the goals of the Horizon 2020–funded SVD@target consortium, which may yield novel powerful SVD biomarkers for future pathogenic and treatment studies.

Fergus Doubal, United Kingdom, Addressed the Questions What Outcomes Matter Most to Patients With SVD and How These Should Be Assessed

Outcomes from trials should be clinically meaningful, biologically plausible, measurable, and sensitive to the treatment being assessed. One method of choosing outcomes is to determine what matters to patients with SVD. Surprisingly, little data for SVD exist and therefore Doubal broadened the scope of his presentation to patients with stroke in general. Outcomes that are important to patients include measures of cognition, function, apathy, fatigue, mood, social functioning, and avoiding death and vascular events. Time spent at home (home time) may be a useful measure post stroke and reflect shorter length of stay and event/admission-free survival. Current qualitative research is ongoing to assess what is important for patients with SVD in trial design and will guide future choice of trial outcomes in patients with SVD.

Session IV: Intracerebral Hemorrhage (Bart van der Worp, The Netherlands, and Charlotte Cordonnier, France)

Rustam Al-Shahi Salman, United Kingdom, Gave an Overview of What He Considered Safe Grounds and Unmet Challenges in Intracerebral Hemorrhage

Low-middle-income countries and hypertension are the priorities when considering how to reduce the global burden of intracerebral hemorrhage (ICH). Incidence seems to be static, and ICH burden is the greatest in low-middle-income countries where ICH is more frequent as a pathological subtype of stroke and the ICH mortality rate is the highest (accounting for ≈75% of all ICH deaths). The population-attributable risk of hypertension for ICH is ≈75%. Lower BP is associated with lower ICH incidence, ICH mortality, case fatality after ICH, and recurrent stroke after ICH. BP variability has emerged as an important predictor of incident stroke and poor outcome after acute ICH, but its prognostic significance for recurrence is unclear. Research into how to best implement measures to reduce BP for both the primary and secondary prevention of ICH is required worldwide. The proportion of people using any antihypertensive drug ≥4 years after a stroke ranges from 13% in low-income countries to 61% in high-income countries, and adequate BP control is rarely achieved. Therefore, an intersectoral approach is required to tackle the social and economic drivers of the undertreatment of hypertension. Potentially modifiable reasons for poor antihypertensive use, poor BP control, and poor secondary prevention of ICH include lack of awareness of hypertension, drug side effects, inconvenience of multiple drugs, variation in the efficacy of antihypertensive drug classes for secondary prevention of stroke, and the absence of systematic approaches for long-term prevention. Therefore, future research should investigate the use of better monitoring of BP (eg, using telemetric techniques) or combinations of antihypertensive drugs that reduce BP variability and are more effective and tolerable in the elderly. Recruitment to randomized controlled trials of ICH prevention interventions is difficult because ICH is relatively rare, ICH affects frail elderly people who have a poor outcome, multinational trials are challenging given inconsistency in requirements for their regulation and conduct, and most treatments have modest effect sizes. Therefore, future ICH randomized trials should optimize their design to maximize recruitment and retention of patients.

David Werring, United Kingdom, Cortical Superficial Siderosis as a Feature of Cerebral Amyloid Angiopathy

Cortical superficial siderosis is a radiological term, describing blood-breakdown product deposition limited to cortical sulci over the cerebral hemispheric convexities, sparing the brain stem, cerebellum, and spinal cord. Although cortical superficial siderosis has many possible causes, previous spontaneous (nontraumatic) convexity subarachnoid hemorrhage from fragile leptomeningeal and cortical vessels is one important mechanism. Cortical superficial siderosis is thus emerging as a novel hemorrhagic feature of cerebral amyloid angiopathy, with relevance for diagnosis, prognosis, and understanding disease mechanisms. In cerebral amyloid angiopathy, cortical superficial siderosis is associated with transient focal neurological episodes and a high risk of future ICH.

Charlotte Cordonnier, France, Addressed the Dilemma of Restarting Antithrombotic Drugs After ICH

Roughly 15% of nontraumatic ICHs occur in patients treated with oral anticoagulants. At discharge, clinicians face a serious dilemma: should they restart oral anticoagulation or not? No randomized evidence is available to date. The risk of rebleeding might be ≥2% to 2.4% per year but may depend on the underlying cause of the ICH. However, the risk of vaso-occlusive events is often underestimated. Randomized trials have recently been launched, such as RESTART and APACHE-AF in the Netherlands.
Karim Klijn, The Netherlands, Explained the Relevance of Secondary Prevention After Spontaneous ICH

Tailored secondary prevention strategies after ICH are urgently needed to diminish the burden of ICH. Such strategies should take into account differences in the risk of recurrent ICH for patients with lobar and nonlobar ICH, the risk ischemic stroke and other vascular events in addition to the risk of recurrent ICH, and the high case fatality of recurrent ICH in comparison with ischemic stroke. In the majority of ICH survivors, the risk of ischemic stroke may be as high as the risk of recurrent ICH. Inadequate BP control has been associated with increased risk of recurrent ICH. Intensive BP treatment is a promising approach that will be studied in the TRIDENT trial (NCT02699645).

Nikola Sprigg, United Kingdom, Highlighted the Potential of Tranexamic Acid After ICH

In patients with ICH, hematoma expansion is common and has been associated with a poor outcome. Tranexamic acid, an antifibrinolytic drug, may reduce the risk of hematoma expansion. It reduced mortality in bleeding patients after trauma in the large CRASH-2 trial. Several clinical trials testing tranexamic acid in patients with ICH are ongoing, and a meta-analysis of the results of these trials is planned. Patients with a spot sign may benefit most from tranexamic acid, but identifying these patients early in clinical trials is proving very challenging.

Session V: Genetics (Convenor: Cathie Sudlow, United Kingdom, and Joan Montaner, Spain)

Martin Dichgans, Germany, Reviewed Advances “From Gene Discovery to Clinical Applications”

Major advances in uncovering the genetic basis of stroke, intermediate phenotypes (e.g., atherosclerosis), and risk factors, such as hypertension, have been achieved. Most of the common variants associated with stroke reside in regulatory DNA. For example, risk variants at HDAC9, the so far strongest risk locus for large-artery atherosclerotic stroke, reside in an intergenic region that shows features of regulatory DNA and are associated with elevated HDAC9 expression. Deficiency of HDAC9 attenuates atheroprorgression in both APOE−/− and LDLR−/− mice, with prominent effects on cholesterol efflux in macrophages. However, this may not be the only mechanism. Efforts to develop class IIa HDAC inhibitors are underway and might represent a new strategy to prevent atherosclerosis. A major lesson from recent genome-wide association studies has been that the risk conferred by individual loci is mostly confined to specific stroke pathogenesis. Conversely, individual loci may contribute to multiple mechanistically related phenotypes. As an example, the HDAC9 gene region is implicated in large-artery stroke, coronary artery disease, and peripheral artery disease. Although genome-wide association studies have identified multiple risk variants for stroke, the clinical use of genotyping common variants for stroke risk prediction is still limited even when using composite scores. However, this may change with ongoing sequencing efforts and the inclusion of variants with larger effect sizes. Another exciting development is the discovery of more and more genes implicated in Mendelian forms of SVDs, most recently the identification of heterozygous mutations in HTRA1 in families with autosomal dominant SVD. Like collagen 4A1/2, another gene implicated in SVDs, HTRA1 forms multimers with defects in multimerization being one potential pathogenic mechanism. The discussion in Garmisch included concepts to restore the assembly and hence function of HTRA1 using genetic approaches.

Hugh Markus, United Kingdom, Responded to the Question “Stroke Pharmacogenomics: Fiction or Future?”

Pharmacogenomics describes how variations in the human genome affect the response to medications and how this allows identifying groups of patients in whom a treatment is efficacious or has side effects. Two examples from stroke highlight potential uses and obstacles to widespread implementation: 5% to 30% of clopidogrel-treated patients exhibit low or no reactivity to clopidogrel. A loss of function CYP2C19 allele correlates with reduced efficacy and was associated with increased events in cardiology trials. This has led to the suggestion that patients with this genotype should be treated with an alternative antiplatelet agent. There are little data in stroke. In warfarin use, pharmacogenomics might allow quicker and more accurate dosing with reduced side effects. CYP2C9 and VKORC1 polymorphisms explain >30% to 40% of the total variation in the final warfarin dose, and genotyping might aid in attaining the optimal dose.

Joan Montaner, Spain, Spoke on “Blood Biomarkers for Stroke: Ready for the Clinic?”

Stroke biomarkers, although not ready for clinical use, belong to the unmet needs in stroke medicine. The troponins of the brain are still to be identified. Proteomics provides an account of the proteome in human brain ischemia and has detected a range of potential candidates. If verified, proteins in blood are promising for the biochemical monitoring of acute stroke. Potential clinical indications include diagnosis of stroke, transient ischemic attacks and mimics, differentiation of stroke subtypes, detection of treatable complications, such as infections, guidance of reperfusion therapies, prediction of stroke outcome and recurrence, and risk prediction of the risk of first-ever stroke. The International Biomarker in Cerebrovascular Diseases (IBCD) study group is actively working in these indications. The most promising results are natriuretic peptides to identify cardioembolic stroke pathogenesis and glial fibrillary acidic protein in combination with other brain injury markers to distinguish ischemic versus hemorrhagic stroke.

Anne Joutel, France, Highlighted the Topic “Restoring Microvascular Function in CADASIL by Genetic Approaches”

TIMP3 and vitronectin bind to Notch3EC and accumulate in Notch3EC-containing deposits on brain vessels of mice and patients with CADASIL. Using genetic interaction approaches in a well-established preclinical mouse model of CADASIL (TgNotch3R169C), it was recently shown that elevated levels of TIMP3 and vitronectin have divergent influences on cerebral blood flow and white-matter lesions. Specifically, genetic
reduction of Timp3 protects against mutant Notch3-induced cerebrovascular dysfunction and genetic reduction of vitronectin ameliorates white-matter lesions. Notably, amelioration of cerebrovascular dysfunction or white-matter lesions in the rescued mice is not associated with a reduction in microscopically detectable Notch3ECD deposits, suggesting that elevated levels of TIMP3 and vitronectin act downstream of Notch3ECD deposition.

Arne Lindgren, Sweden, Reviewed the “Genetics of ICH”
Genetic factors influence both risk and outcome of ICH. Monogenic variants related to ICH risk include Marfan syndrome, von Hippel–Lindau syndrome, COL4A1-related brain SVD, hereditary hemorrhagic telangiectasia (Osler–Weber–Rendu disease), hereditary cerebral amyloid angiopathy, and cerebral cavernous malformations. Family studies and genome-wide complex trait analysis indicate partial heritability of the common phenotypes of deep ICH and lobar ICH. APOE alleles ε2 and ε4 have been related to lobar ICH risk and ε4 allele also to deep ICH risk. Single-nucleotide polymorphism in the COL4A2 gene, in the 1q22 region, as well as a genetic risk score based on 38 single-nucleotide polymorphisms related to BP, have been associated with nonlobar ICH risk. Outcome after ICH may also be influenced by genetic variations. People with lobar ICH carrying the APOE ε2 allele show increased mortality and poor functional outcome. More research is needed to better understand genetic factors influencing risk and outcome of ICH and to prevent and treat ICH.

Session VI: Stroke in the Young (Bo Norrving, Sweden, and Valeria Caso, Italy)
Jukka Putaala, Finland, Gave a Key Note Lecture on “Juvenile Stroke: Size of the Problem and Challenges Ahead”
Ischemic strokes at younger ages are increasing. In high-income countries, one fourth of ischemic strokes occur in economically active individuals. Globally, almost half of the entire stroke burden affects young people because the young have a greater likelihood to survive with long-life spans ahead and because strokes in low- and middle-income countries occur at younger ages than in high-income countries. Vascular risk factors are highly prevalent in young adult patients with stroke, and early-onset vascular risk factors may represent more aggressive forms of these comorbidities, yet the strength of association of such risk factors has received little attention. Furthermore, young adults with ischemic stroke often harbor risk factors with weak or uncertain association; of which, most can be considered young age specific (eg, reproduction-related factors, migraine, patent foramen ovale, shift work, and illicit drug use). Relatively high rates of atherosclerotic changes have been detected in the young, and the pathogenetic spectrum of young stroke populations may begin to resemble the older ones. However, despite the increasing number of vascular risk factors and prevalent atherosclerosis, in ≤50% young patients, a definite cause of their ischemic stroke cannot be identified. Long-term follow-up studies of young adult strokes show higher than expected overall mortality, high rate of deaths caused by vascular causes, and high risks of recurrent strokes and vascular disease for years to come. Although there is scarce evidence to support secondary prevention decisions in young adults, the high numbers of events during follow-up indicate an active pathology underlying most early-onset strokes. Future studies should focus in particular on uncovering the reasons for the increasing incidence of early-onset strokes, elucidate the special features of early-onset vascular risk factors, and decipher the less well-documented young age–specific risk factors and their relationship with the hidden stroke mechanisms.

Jérôme Mawet, France, Discussed Data on the “Causes and Course of Reversible Cerebral Vasconstriction Syndrome”
Reversible cerebral vasconstriction syndrome is characterized by severe acute, mostly thunderclap headaches and multifocal constrictions of cerebral arteries resolving spontaneously. Seizures and focal neurological deficits related to cortical subarachnoid hemorrhage, ICH, ischemic stroke, and posterior reversible encephalopathy syndrome may occur. The diagnosis of reversible cerebral vasconstriction syndrome should thus be considered in a large variety of acute cerebrovascular conditions. Furthermore, the cooccurrence of cervical artery dissection (CeAD) and reversible cerebral vasconstriction syndrome and the evidence of ischemic stroke related to reversible multifocal constrictions of cerebral arteries in subjects with moderate or even without headache suggest that the spectrum of reversible cerebral vasconstriction syndrome is larger than previously thought.

Jens Dreier, Germany, Addressed the Provocative Question “Stroke and Spreading Depression—Still at the Bench?”
Spreading depolarizations (SDs) are waves of near-complete breakdown of neuronal transmembrane ion gradients, the largest possible pathophysiologic disruption of viable cerebral gray matter, and an essential mechanism of lesion development. SDs are increasingly recorded in the framework of multimodal neuromonitoring in neurointensive care and offer hope to provide a diagnostic summary measure of metabolic failure and excitotoxic brain injury. After injury, spontaneous SDs can arise continuously for hours to days because of energy supply–demand mismatch in metabolically compromised but viable tissue. Such spontaneous SDs can trigger additional neuronal injury through decreased perfusion (spreading ischemia) and prolonged ionic breakdown.

Stephanie Debette, France, Addressed the Question “CeADs and Genetics: Where to Now?”
Recent genome-wide association studies found a common variant in PHACTRI to be associated with the risk of CeAD. The same risk allele was further shown to be associated with a lower risk of migraine and with an increased risk of myocardial infarction. Efforts to decipher this pleiotropy may provide important information on the biological underpinnings of these disabling conditions. Moreover, expanding the study of CeAD genetics by larger, transethnic genome-wide
association studies and exploring the role of rare variants with next-generation sequencing will be important. Finally, despite their rare occurrence, familial cases of CeAD may provide complementary information on genes and biological pathways involved in CeAD.

Frank-Erik de Leeuw, The Netherlands, Provided an Update on “Long-Term Prognosis After Young Stroke—Can We Tell?”

Stroke in young adults (18–50 years) often occurs in a decisive period of life with respect to family and professional career planning. Reliable information particularly on the long-term prognosis is therefore essential in balanced decision making. The FUTURE study from the Netherlands indicates a 3 to 4-fold increased risk of mortality during 20 years of follow-up.50 Every third participant had a recurrent vascular event.51 Also, functional prognosis is relatively poor. About 1 in 8 survivors was dependent in activities of daily living, even 10 years after their stroke. This, in part, explained the high proportion of 40% unemployment among stroke survivors, about 8x more than in the general Dutch population.55 In addition, female survivors have more often pregnancy complications (HELLP, still births) than their healthy counterparts.

Session VII: Cognition and Hot Topics

(Kennedy Lees, United Kingdom, and Martin Dichgans, Germany)


There is a high and continuously increasing incidence of dementia after stroke, which may be underestimated because of baseline selection biases, attrition, and the applicability of cognitive testing.56 Moreover, cognitive impairment is a continuum with vascular dementia as the most severe part of the clinical spectrum and with many patients having mixed pathologies. As patients with cognitive impairment after stroke have a poorer prognosis, it is important to assess cognition. Brief cognitive screening tests, such as the MMSE and MoCA, are practical and accurate for the detection of cognitive impairment.57 These may be supplemented by additional tests to improve accuracy. However, it remains important to establish the local validity of screening tests using more comprehensive test batteries as proposed by the NINDS-CSN. Furthermore, it is crucial to set appropriate criteria for the number of impaired tests so as to maintain a low false-positive rate.

Patients with stroke can be assessed for cognitive impairment subacutely despite issues arising from acute stroke-related effects. The traditional time window for assessment of cognitive function is 3 to 6 months post stroke so as to allow time for recovery. Although it may not be practical to comprehensively assess all patients, the use of brief screening tests is recommended as there are potential benefits for management and clinical trials. Cognitive assessment using brief screens should also be considered annually in high-risk patients who are also at risk of silent stroke affecting cognition.

Perttu Lindsberg, Finland, Discussed “Basilar Artery Occlusion: Drip, Ship, Retrieve?”

Stentriever achieves ≤100% recanalization results in basilar artery occlusion, but the diagnosis is often delayed. The brain stem can be permanently ischemic already on admission to a stroke center, resulting in futile recanalization if treated aggressively.58 The crucial question is whether more basilar artery occlusion patients should receive intravenous thrombolysis after computed tomographic angiography and then be shipped to stroke centers for thrombectomy. Data from open series suggest that early intravenous thrombolysis recanalizes 4 to 7 in 10 cases of basilar artery occlusion. Ample collaterals can individually prolong the therapeutic time window beyond 12 hours. In the absence of extended baseline infarction, on-demand thrombectomy at stroke centers is probably beneficial.


Poststroke infections are common and associated with poor functional outcome. A burning clinical question was if preventive antibiotics affect functional outcome. The Preventive Antibiotics in Stroke Study (PASS) conducted in the Netherlands included 2550 patients.59 Despite a significant effect on the poststroke infection rate, functional outcome did not improve. STROKE-INF, a cluster randomized trial from the United Kingdom, revealed similar results. Therefore, immediate treatment of infection when symptoms arise succeeds for the majority of patients in clinical routine. In severe strokes, preventive antibiotics may still have a role, a question that will be explored in the EU-wide PRECIOUS trial.

Thorsten Steiner, Germany, Gave an Update on European Stroke Organization Guidelines

European Stroke Organization has published a standard operating procedure for the development of guidelines. The approach follows the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology.60 The procedure involves European Stroke Organization members in making suggestions for topics and getting involved in guideline production. European Stroke Organization has performed 3 workshops to train guideline work group members in the use of the GRADE system. Two guidelines after the new approach have been published, 3 will be published in spring 2016, and another 9 are currently in development.

Adam Denes, Hungary, Showed the “Microglia Control Neuronal Excitability In Vivo”

Microglia are the main immune cells of the brain, and neuronal network activity is monitored and controlled by microglia. However, it is unclear whether microglia control the survival of injured neurons via shaping the activity of complex neuronal networks in vivo. Selective elimination of microglia leads to markedly increased infarct size, which is reversed by microglial repopulation. The absence of microglia results in dysregulated neuronal calcium responses and accelerates calcium overload in the injured brain, associated with the absence of SD. Thus, microglia are identified as major regulators of...
neuronal excitability and SD in vivo, with potential implications for ischemic and common brain diseases.

Werner Hacke, Germany, Argued for “New Study Designs for Acute Stroke”

The stroke community applies possibly excessive rigor to its trials, demanding randomization of broad populations with parallel controls and a significance threshold of 5%. Werner Hacke argued for a different approach, maintaining high trial quality on randomization, blinding, monitoring, safety reporting, and in-person end point assessment but reducing the number of patients in general and controls in particular by extensive selection, concentrating on high informative patient cohorts. He suggested that 2:1 or 3:1 active/control randomization, a significance threshold of 10%, pooling of controls from several trials, individual patient interim meta-analysis of ongoing trials, and sequential testing approaches should be combined to identify useful treatments more readily.

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Disclosures

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References

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PROGRAMME

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Conference Chairs: Heinrich Mattle, Martin Dichgans

Organizing Committee: Martin Dichgans (Munich), Kennedy Lees (Glasgow), Heinrich Mattle (Bern), Bo Norrving (Lund), Anna Planas (Barcelona), Bart van der Worp (Utrecht), Joanna Wardlaw (Edinburgh)

Thursday, 19 November 2015

18.00 Welcome address:
   Heinrich Mattle, Bern, Switzerland & Martin Dichgans, Munich, Germany

18.10 Chairman: Werner Hacke, Heidelberg, Germany

Keynote lecture How much can we improve secondary prevention of stroke by better use of existing treatments?
18.10 – 19.10 Peter Rothwell, Oxford, United Kingdom

19.40 Welcome Dinner

Friday, 20 November 2015

7.00 – 8.00 Breakfast

Session I Stroke Immunology
8.00 – 9.45 Convenor: Anna Planas, Barcelona, Spain
   Co-Chair: Ulrich Dirnagl, Berlin, Germany

8:00 Opening remarks

Keynote lecture Avenue for treatment or false promise?
8:05 Nancy Rothwell, Manchester, United Kingdom
8:35 Brief open discussion

8:40 1. Brain-gut-microbiome interaction in stroke
     Arthur Liesz, Munich, Germany
8:50 2. TREM2 in ischemic stroke
     Midori Yenari, San Francisco, USA
9:00 3. Lectin pathway and the complement system
     Grazia De Simoni, Milan, Italy
9:10 4. Molecular imaging of brain-immune interactions
     Denis Vivien, Caen, France
9:20-9:45 Open discussion

9:45-10:15 Coffee break

**Session II**

**Acute Stroke Treatment / Endovascular Therapy**

10.15 -12.00

Convenor: Heinrich Mattle, Bern, Switzerland

Co-Chair: Alain Bonafé, Montpellier, France

10:15 Opening remarks

Keynote lecture  Where are we heading after MR. CLEAN, ESCAPE, EXTEND-IA, REVASCAT, and SWIFT-Prime?

10:20 Diederik Dippel, Rotterdam, The Netherlands

10:50 Brief open discussion

10:55 1. Who should be sent for endovascular treatment?

Simon Jung, Bern, Switzerland

11:05 2. Devices and techniques for mechanical recanalization

Olav Jansen, Kiel, Germany

11:15 3. New territory infarcts - how to assess, how to prevent?

Jan Gralla, Bern, Switzerland

11:25 4. Conscious sedation or general anesthesia?

Alain Bonafé, Montpellier, France

11:35-12:00 Open discussion

12:00-14:00 Lunch and time for recreational activities

**Session III**

**Small Vessel Disease**

14.00 – 15.45

Convenor: Martin Lauritzen, Copenhagen, Denmark

Co-Chair: Jan Geert Biessels, Utrecht, The Netherlands

14:00 Opening remarks

Keynote lecture  Lacunar stroke: How to diagnose and how to treat

14:05 Oscar Benavente, Vancouver, USA

14:35 Brief open discussion

14:40 1. Predictors of clinical progression in CADASIL: relevance to sporadic SVDs

Hugues Chabriat, Paris, France

14:50 2. What outcomes matter most to patients with small vessel diseases and how should these be assessed?

Fergus Doubal, Edinburgh, United Kingdom

15:00 3. Role of pericytes in regulating cerebral blood flow

Martin Lauritzen, Copenhagen, Denmark

15:10 4. Innovative imaging of human microvessels in vivo: structure and function

Jeroen Hendrikse, Utrecht, The Netherlands

15:20-15:45 Open discussion

15:45-16:15 Coffee break
Session IV  Intracerebral hemorrhage
16.15 – 18.00  Convenor: Bart van der Worp, Utrecht, The Netherlands
               Co-Chair: Charlotte Cordonnier, Lille, France

16:15  Opening remarks

Keynote lecture  What hope for ICH randomised trials?
16:20  Rustam Al Shahi Salman, Edinburgh, United Kingdom
16:50  Brief open discussion

16:55  1.  CAA and cortical superficial siderosis
       David Werring, London, United Kingdom
17:05  2.  Restarting antithrombotic drugs after ICH
       Charlotte Cordonnier, Lille, France
17:15  3.  Other secondary prevention after ICH
       C.J.M. Karin Klijn, Nijmegen, The Netherlands
17:25  4.  Tranexamic acid after ICH
       Nikola Sprigg, Nottingham, United Kingdom

17:35-18:00  Open discussion
18:00  Adjourn
18:45  Special lecture – speaker and title tbc
19.45  Banquette Dinner

Saturday, 21 November 2015

7.00 – 8.30  Breakfast

Session V  Genetics
8.30 – 10.15  Convenor: Cathie Sudlow, Edinburgh, United Kingdom
              Co-Chair: Joan Montaner, Barcelona, Spain

8:30  Opening remarks

Keynote lecture  From gene discovery to clinical applications
8:35  Martin Dichgans, Munich, Germany
9:05  Brief open discussion

9:10  1.  Pharmacogenetics: fiction or future?
       Hugh Markus, London, United Kingdom
9:20  2.  Blood biomarkers for stroke: ready for the clinic?
       Joan Montaner, Barcelona, Spain
9:30  3.  Restoring microvascular function in CADASIL by genetic approaches
       Anne Joutel, Paris, France
9:40  4.  Genetics of intracerebral hemorrhage
       Arne Lindgren, Lund, Sweden
9:50-10:15  Open discussion
10:15-10:45  Coffee break

Session VI  Stroke in the Young
10.45 -12.20  Convenor: Bo Norrving, Lund, Sweden
Co-Chair: Valeria Caso, Perugia, Italy

10:45  Opening remarks

Keynote lecture  Juvenile stroke: Size of problem and challenges ahead
10:50  Jukka Putaala, Helsinki, Finland
11:20  Brief open discussion

11:25  1. Encoding the cause and course of Reversible Cerebral Vasoconstriction Syndrome
       Jérôme Mawet, Paris, France
11:35  2. Stroke and spreading depression – still at the bench?
       Jens Dreier, Berlin, Germany
11:45  3. Cervical artery dissections and genetics: where to now?
       Stephanie Debette, Bordeaux, France
11:55  4. Long term prognosis after young stroke - can we tell?
       Frank-Erik de Leeuw, Nijmegen, The Netherlands

11:55-12:20  Open discussion

Session VII  Cognition and Hot Topics
12.20 -13.30  Convenor: Kennedy Lees, Glasgow, United Kingdom
Co-Chair: Martin Dichgans, Munich, Germany

Keynote lecture  Cognitive testing in stroke: why, when, and how?
12:20  Chris Chen, Singapore
12:50-12:55  Brief open discussion

13:00  Hot Topics in 5 minutes sharp

1. Basilar artery occlusion: drip?, ship?, retrieve?
   Perttu Lindsberg, Helsinki, Finland

2. When to choose antibiotics in stroke
   Paul Neederkorn, Amsterdam, The Netherlands

3. Update on ESO Guidelines
   Thorsten Steiner, Frankfurt, Germany

4. Microglia control neuronal excitability in vivo
   Adam Denes, Budapest, Hungary

5. A call for new study designs in stroke trials
   Werner Hacke, Heidelberg, Germany

13:25-13:35  Adjourn and farewell
   Martin Dichgans, Munich, Germany & Heinrich Mattle, Bern, Switzerland

13:35-14:00  Late lunch and departure
The European Stroke Science Workshop 2015 is supported by the German Research Foundation (DFG; DI 722/12-1), the Munich Cluster for Systems Neurology (SyNergy), Munich, and Daiichi-Sankyo Europe GmbH.
Your Notes
SAVE THE DATE