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Contents

Presidential symposium

Brain ischaemia, new patterns and treatments

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White matter ischaemic syndromes
M. Hennerici
Mannheim, D

Subcortical nuclear and white matter ischaemic lesions have long been known to present with less impressive signs and symptoms and cortical ischaemia: these reange from a) often clinically asymptomatic, incidental findings once CT-/MRI studies are performed through b) occasionally oligosymptomatic, uncharacteristic patterns (in particular if overlap exists in diaschisis) to c) few very typical lesions if nuclear structures are heavily involved (brainstem, thalamus, lentiform nuclei etc). Isolated white matter lesions, manifest mostly once disseminated chronic ischaemia occurs as subcortical vascular encephalopathy (SVE), if remote focal strokes coincidentally happen in synergistics syndromes or due to large sensory-motor tract disruption in severe lacunar strokes. Etiologies are widespread and overlap with many other white matter diseases ranging from multiple sclerosis in the younger to cerebral amyloid angiopathy in the elderly often with unknowen mechanisms as far as neurodegeneration is concerned (Alzheimer's disease, CJD, "paraneoplastic syndromes" etc). This review concentrates on probably the only "vascular" type dementia studied intensively during recent years and attempts to demonstrate potentials of insight to be achived not only for a better understanding of such diseases in increasingly older populations but also what can be tranferred to other diseases still difficult to understand today.

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Present and future of acute stroke therapy
M. Fisher
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The current status of acute stroke therapy remains limited to one approved drug, intravenous (i. v.) tPA initiated within 3 hours of stroke onset. This limited therapeutic armamentarium is reflected by the small number of acute ischemic stroke (AIS) patients that are currently treated. Other strategies for the use of thrombolytic therapy in AIS, such as intraarterial delivery of the thrombolytic agent, combined i. v. and i. a. therapy and the use of other thrombolytic agents are being explored. Thrombolytic therapy is directed at restoring or improving blood flow to the ischemic brain, but not at ameliorating the consequences of ischemia within brain tissue related to reduced or absent blood flow, i. e. the ischemic cascade. Recent advances regarding thrombolytic therapy have occurred. Intravenous Desmoteplase was shown to improve cerebral perfusion and tended to improve clinical outcome in two small trials with a 3–9 hour treatment window. A larger trial with a 9-hour treatment window is underway. In the DEFUSE study of i. v. t-pa given between 3–6 hours after stroke onset, patients with a diffusion/perfusion mismatch benefited from treatment while those without mismatch did not. This observation supports the results of several observational studies that demonstrated apparent clinical benefit with i. v. t-pa when given 3–6 hours after stroke onset in patients with an MRI-confirmed mismatch. In the United States, the MERCI clot retrieval device has been approved for removing thrombi from intracranial vessels but not as a stroke treatment. Concerns remain about the safety of this device and further clinical trials and registries should provide additional information about safety and efficacy

Drugs directed at the ischemic cascade are termed neuroprotectants and many different types of neuroprotective drugs have been developed targeted at the manifold aspects of ischemic brain injury. Many neuroprotective drugs were evaluated in advanced clinical trials, but until recently all of these trials were not positive for a variety of reasons. No neuroprotective drug is currently available for clinical use. In the recently reported SAINT-1 trial of the spin-trap agent, NXY-059 a positive effect on the primary outcome measure was observed. The primary outcome measure was a shift of the modified Rankin scale of at least one point across the whole range of the scale and not a dichotomized outcome as was used in all previous AIS trials. This outcome measure is targeted to look for a modest but likely clinically meaningful treatment effect as opposed to a "cure" when the goal was to assess the percentage of patients with little or no deficit, i. e. Rankin 0–1. In future AIS trials it is likely that the Rankin shift approach will be used as the primary outcome measure. In the SAINT-1 trial no effect was observed on the change from baseline to day 90 on the NIHSS scale but efficacy trends were observed on other relevant outcome measures. The ongoing SAINT-2 trial will provide vital information about the efficacy or lack thereof on NXY-059.

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Penumbra is brain: targeted neuro-imaging in hyperacute stroke
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Given the millions of neurons dying every hour in acute ischemic stroke, we need more advanced methods to treat the appropriate patient with the appropriate method. Shortening symptom-to-treatment delays is mandatory for all stroke patients, but clinicians and scientists have recognized for quite a while that stroke is highly variable from one individual to the other. This applies particularly to the amount of irreversibly damaged and salvageable tissue ("core" and "penumbra") and to the localisation of arterial occlusions.

Measuring tissue perfusion with various methods (PET, SPECT, Xenon-Ct, PWI-DWI MRI, perfusion-CT etc.), we are recognizing that time is not the gold standard but a surrogate marker when it comes to predicting the presence of penumbra. Mounting evidence, most recently from the DEFUSE trial, confirms that patients without penumbra do not benefit from recanalisation, and may even be harmed. On the other hand, the DIAS trial has shown that patients may benefit from thrombolysis well beyond the 3 hour limit if they have a persistent penumbra. These data strongly support the notion that "penumbra is brain" rather than "time is brain", and that the time clock should be replaced by a pathophysiological clock in most patients when it comes to acute treatment decisions.

The second, similarly important requirement for successful stroke treatment is rapid, complete, and persistent recanalisation. Early recanalisation, whether spontaneous or treatment-related, has been associated in most studies with better radiological and clinical outcomes. We therefore should use all efforts available to recanalize arteries in acute stroke.

Thirdly, advanced neuroimaging may predict of the neurovascular complications. Examples are haemorrhagic transformation in patients with severe and large volume ischemia who recanalize rapidly, or mass effect from brain ischaemia. When data about perfusion and arterial imaging are combined, the best stroke outcomes occur as expected in patients with a small core, a large penumbra and early recanalisation. Although not proven yet, it is likely that neuroprotective treatments will be particularly effective in exactly the same population, because the therapeutic agents are more likely to reach their intended target.

Which acute neuroimaging technique should we use to identify the treatable patient? Plain CT main be a suitable screening tool for non-invasive recanalisation and neuroprotection in the very early phase (< 90 min. or so), where it can be assumed that most patients have a significant penumbra. Thereafter, perfusion-imaging and arterial imaging becomes essential, either to decide about the indication and contraindications of different recanalisation and neuroprotective strategies, or to decide about further treatment in patients who have undergone ultra-early (< 90 min) treatment based on a plain CT. Both perfusion-MRI our perfusion-CT reliably detect and distinguish reversible from irreversible ischemia. For imaging of arterial pathology, CT- and MR-angiography are similary accurate, and transcranial Doppler/Duplex may be a valuable alternative. Only few centers now take the risk of performing conventional angiography without first doing a non-invasive study in candidates for intraarterial therapy.

Ideally, all these advanced imaging methods should be available 24/24hours. The technique that fits the patient (contraindications, availability) and his doctor (experience, availability) most may be then be chosen as the "best" imaging in a given situation.

Symposium

Neurology of sleep

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Sleep and synaptic plasticity
G. Tononi
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Background: This paper will discuss a novel hypothesis – the *synaptic homeostasis hypothesis* – which claims that sleep plays a role in the regulation of synaptic weight in the brain [1]. In brief, the hypothesis is as follows: 1. Wakefulness is associated with synaptic potentiation in several cortical circuits; 2. Synaptic potentiation is tied to the homeostatic regulation of slow wave activity; 3. Slow wave activity is associated with synaptic downscaling;

4. Synaptic downscaling is tied to the beneficial effects of sleep on neural function and, indirectly, on performance.

Methods: Evidence for the hypothesis has been obtained using many experimental paradigms, from molecular studies of sleep and wakefulness to neuroimaging studies in humans.

Results: The synaptic homeostasis hypothesis can account for several aspects of sleep and its regulation, and several of its specific predictions were confirmed experimentally.

Conclusions: According to the hypothesis, plastic processes occurring during wakefulness result in a net increase in synaptic strength in many brain circuits. The role of sleep is to downscale synaptic strength to a baseline level that is energetically sustainable, makes efficient use of gray matter space, and is beneficial for learning and memory. Thus, sleep is the price we pay for plasticity, and its goal is the homeostatic regulation of the total synaptic weight impinging on neurons. The hypothesis accounts for a large number of experimental facts, makes several specific predictions, and has implications for sleep, neurological, and psychiatric disorders.

Supported by NIH Director Pioneer Award

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Sleep apnoea and cardiovascular diseases
P. Lavie
Technion-Israel Institute of Technology, Lloyd Rigler Sleep Apnea Research Laboratory (Haifa, IL)

Obstructive sleep apnea characterized by intermittent and recurrent pauses in respiration during sleep resulting in a decreased oxygen saturation and sleep fragmentation is closely associated with cardiovascular morbidity and mortality. Sleep apnea has been shown to be causally related with hypertension and to be associated with strokes, ischemic heart diseases and cardiac arrhythmias. Evidence accumulated in recent years shed a new light on the natural evolution of cardiovascular morbidity in obstructive sleep apnea. Several studies demonstrated the existence of endothelial dysfunction and early clinical signs of atherosclerosis in patients with sleep apnea who were free of any overt cardiovascular diseases. This suggests that the cardiovascular morbidity in sleep apnea is developing over several years through accumulated damage to the vasculature. Research performed in our laboratory has focused on the pathophysiology of atherogenic processes in sleep apnea syndrome. We showed that hypoxia/reoxygenation, that is the most important characteristic of sleep apnea, promotes the formation of reactive oxygen species that activate critical redox-sensitive signaling pathways and transcription factors. This facilitates the expression of sets of genes that encode proteins essential to adaptation to hypoxia, as well those that elicit inflammatory pathways such as adhesion molecules and inflammatory cytokines. Consequently, inflammatory and immune responses are activated thus resulting in the activation of endothelial cells/leukocytes/platelets. These activated cells express adhesion molecules and pro-inflammatory cytokines that in turn may further exacerbate inflammatory responses and cause endothelial cell injury and dysfunction. This newly acquired insight into the pathophysiology of cardiovascular morbidity in OSA have important implications regarding the diagnosis and treatment of the syndrome.

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Narcolepsy
C. L. Bassetti
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Narcolepsy is a life-long, usually sporadic (rarely familial) sporadic which usually starts in the 2. or 3. decade of life. The prevalence of narcolepsy is similar to that of multiple sclerosis (about 1:2000 in the adult population).

Excessive daytime sleepiness (EDS) is usually the first and most disabling symptom. Cataplexy – a sudden and short loss of muscle tone triggered by emotions with preserved consciousness – is the only pathognomonic symptom of narcolepsy and shares features with physiological REM sleep atonia. Associated, non specific symptoms of narcolepsy include sleep paralysis, hallucinations, parasomnias, weight gain, and psychosocial disability. Biological markers of narcolepsy are diagnostic helpful and include 1) a specific HLA class II-subtype (DQ1*0602, 90–95 % of patients), 2) the appearance of REM-sleep within 15–20 minutes after sleep-onset (sleep onset REM, 70–80 %), and 3) the absence/reduction of the recently discovered hypothalamic peptide hypocretin-1 (orexin A, 90 %) in the cerebrospinal fluid.

Narcolepsy usually arises from a combination of genetic and -yet to be identified- environmental factors. In fact, only about one third of monozygotic twins are concordant for the disease. Less commonly, genetic factors (familial narcolepsy) or acquired brain disorders (symptomatic narcolepsy) prevail. Narcolepsy is associated with multiple neurotransmitter signalling deficiencies (hypocretin, dopamine, dynorphine, neuronal activity-regulated pentraxin, ...). Based also on studies in rodent and canine models of the disease, narcolepsy is thought to be due to an instability of sleep-wake mechanisms with rapid transitions between wakefulness, NREM and REM sleep and appearance of dissociated states (in which elements of different states intermingle).

Treatment of narcolepsy is successful in the majority of patients and include information/counselling; scheduled naps; stimulants (e. g. modafinil, methylphenidate); and anticataplectic drugs (e. g. clomipramine, sodium oxybate).

Future research will clarify the possibility of an autoimmune origine of narcolepsy, the exact correlation between signalling deficiencies and clinical manifestations, and the value of new treatment strategies (hypocretin agonists, immunomodulation).

Imaging brain diseases

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Movement disorders
D. J. Brooks
Imperial College (London, UK)

This talk will review findings obtained in movement disorders with recent advances in neuroimaging technology. Application of advances in magnetic resonance imaging such as voxel based morphometry, transcranial sonography, diffusion weighted and magnetization transfer MRI, to parkinsonian syndromes and dystonia are highlighted. The role of postron emission tomography to detect microglial activation in Parkinson's and Huntington's disease and measure changes in synaptic dopamine levels is also featured. Finally, some future directions in neuroimaging are presented.

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Spinal cord disorders
M. Forsting
Department of Diagnostic and Interventional Radiology and Neuroradiology, University Hospital of Essen (Essen, D)

Spinal cord disorders include a huge variety of totally different diseases starting from congenital malformations over non-neoplastic disorders and ending with tumours and tumour-like lesions of the spinal cord.

Congenital anomalies of the spinal cord include open spinal dysraphism, occult spinal dysraphism and anomalies of abnormal canalisation and retrogressive differentiation of the cord.

Non-neoplastic disorders start with infectious diseases like spondylitis, epidural and subdural infections and spinal cord abscesses. As in the brain demyelating diseases can occur within the spinal cord as well as vascular problems like spinal cord ischemia and different kinds of vascular malformations. Specifically in young age patients spinal cord injuries are important and have to be diagnosed accurately.

Intramedular tumours are usually not benigne and most of them are either astrocytomas or ependymomas. The talk will focus on vascular diseases of the spinal cord and tumour- and tumour-like lesions.

The imaging modality of choice for all spinal cord lesions is nowadays clearly MR including MR-angiography. Specifically for vascular malformations the classical DSA is often still mandatory and sometimes endovascular therapy is the matter of choice in vascular malformations of the spinal cord.

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Cerebrovascular disorders
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Recent advances of modern imaging technology have greatly expanded our capabilities for the in-vivo assessment of cerebrovascular disorders. In this context treatment-oriented optimization of acute stroke imaging certainly has remained the foremost challenge. The importance of more slowly progressing and diffuse vascular brain damage, however, is now also increasingly recognized.

With constant improvement of CT scanners and increasing experience of interpreters, CT nowadays not only serves to rule out intracerebral or subarachnoid bleeding but can display changes indicative of ischaemic damage already within the first hours after stroke. Nevertheless, magnetic resonance imaging (MRI) clearly surpasses the sensitivity for acute ischaemic damage,

and it is especially diffusion weighted imaging (DWI) that has revolutionized stroke imaging by allowing to depict morphologic brain changes as early as 1 hour after the acute event. Concerns that MRI may fail to depict intracerebral hemorrhage as accurately as CT have also been ruled out. DWI is especially helpful in depicting small acute ischaemic lesions and to separate them from old cerebral damage. This helps to improve clinicoradiologic correlations and can add important information regarding specific stroke mechanisms. Similar to the concepts of "ischaemic penumbra" a mismatch between the abnormality seen on DWI and that indicated by perfusion-weighted MRI can serve to identify threatened but still salvageable tissue and thus may help to extend the time window of successful acute thrombolysis and for guiding more complex treatment decisions.

The sensitivity of MRI for subtle tissue changes has also served to increasingly recognize the importance of chronic vascular damage most often from microangiopathy which appears to threaten brain functioning in a more global manner. Abnormalities consist of diffuse white matter changes, silent lacunes and infarcts and there is evidence that vascular damage may even promote brain shrinkage. Specific MRI pulse sequences also allow the detection of remnants of minimal blood seepage through damaged intracerebral vessels which is likely to be an indicator of more pronounced microangiopathy. All these abnormalities have been shown to progress over time and are associated with increasing cognitive impairment up to full-blown dementia as well as gait disorders and a higher probability for falls in the elderly. Finally, there is evidence for an association between small-vessel disease-related brain tissue changes and mood disorders especially depression. Efforts to also prevent chronic vascular damage thus become more and more important as its frequency increases in parallel with the life expectancy of western populations.

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Brain imaging in dementia
M. Filippi
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The review of all possible dementing conditions and all imaging techniques used to investigate their structural and functional substrates is beyond the scope of the present abstract. As a consequence, this abstract is focussed on the use of magnetic resonance imaging (MRI) in the study of Alzheimer's disease (AD), as a model for cortical dementia, and multiple sclerosis (MS), as a model for subcortical dementia.

AD is the most common form of age-related dementia and affects approximately 1–5% of the population over 65 years. In AD, seminal conventional MRI (cMRI) studies have shown the presence of gray matter (GM) loss, mainly in the medial temporal structures. Hippocampal size reduction was also found in patients with mild cognitive impairment (MCI) and was predictive for subsequent transition to AD. The atrophy process later spreads to associative temporo-parietal and frontal cortical areas. However, the correlation between regional GM atrophy and global cognitive impairment is relatively weak, suggesting that other pathological processes are at work. Non-conventional MRI techniques have indeed shown that AD also causes marked microstructural damage to the residual GM and that the combined quantification of GM loss and intrinsic damage is strongly correlated to the severity of cognitive impairment. Normal-appearing (NA) WM regions linked to associative cortices are also damaged and the severity of such damage is strongly related to AD cognitive decline. In MCI, damage to the NA brain tissue is intermediate between those of normals and AD patients, suggesting that WM and GM microstructural abnormalities are early events in AD. Functional MRI (fMRI) studies with cognitive tasks suggested that significant functional cortical changes also occur in AD patients with the potential to limit the clinical outcome of the underlying tissue damage.

Cognitive impairment affects approximately 40–70% of patients with MS. In these patients, the extent of WM lesions visible on cMRI scans, and their location in the hemispheric WM were found to be associated moderately with the level of neuropsychological performances. Linear and volumetric MRI-derived quantities reflecting brain parenchymal loss in general and neocortical tissue loss in particular were found to be correlated with neuropsychological test scores and with comprehensive cognitive impairment indexes, at a greater magnitude than the corresponding lesion volumes. More recently, the use of non-conventional MRI techniques has shown that subtle changes to the NAWM, overall intrinsic GM pathology and intrinsic T2-visible lesion damage also contribute to MS-related cognitive impairment. In fMRI studies with cognitive tasks, MS patients contrasted to matched normal controls exhibit different distribution and extent of cortical activations and this is believed to have, at least partially, a compensatory role, which contributes in limiting the neuropsychological manifestations of the disease.

All these observations suggest that the in-vivo assessment through imaging-based technology of factors contributing to the cognitive decline associated to the different potentially dementing neurological conditions is a rather complicated business. Such an assessment would require a careful assessment of the extent of tissue loss and the status of the remaining tissue in the different brain compartments, as well as the role of compensatory mechanisms.

New trends in treatment of neurological disorders

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Specific and aspecific immune interventions in multiple sclerosis
G. Comi
IRCCS San Raffaele (Milan, I)

Immunomodulating and immunosuppressive treatments for multiple sclerosis patients are directed against the inflammatory process and are only partially effective. This partial failure could be explained by mechanisms of axonal damage at least partially independent from acute or chronic inflammation. This suggests that there is a need for better use of available treatments and the necessity of alternative new therapeutic options to halt disease progression and enhance recovery mechanisms. Concerning actual treatments, two strategies are quite interesting: early treatment and combination therapy. The former approach is based on converging epidemiological, immunological and pathological studies and is proved by some recent clinical trials. The second one is under evaluation on ongoing clinical trials. Progress in understanding the mechanisms of T cell activation, inactivation and modulation has been translated into new therapeutic strategies aiming at inducing selective immunosuppression. Such an approach is now tested in phase II-III clinical trials.

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Alzheimer's amyloid immunotherapy
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Accumulation of aggregated beta-amyloid protein in strategic areas of the cerebral cortex is associated to Alzheimer's diseaise (AD) in the common sporadic form of the elderly as well as in the rare heredidary forms.

Schenk et al. (1999) were able, in a milestone experiment, to prevent and even partly revert the amyloid burden and the associated neuropathological changes, in the brain of transgenic mice expressing the human amyloid protein involved in MA, by active anti-amyloid immunization. This remarkable result was shortly after replicated by other groups, either by active immunisation with the human aggregated A-beta or a passive immunization with anti A-beta monoclonal antibodies.

A phase 1 study in 20 healthy volunteers of single doses of the Elan aggregated amyloid antigen was first conducted in the USA, with excellent tolerability except minor local reactions at the site of intra-muscular injection (Elan, data on file).

Then a phase 2a randomized trial was carried on in 84 patients with AD, in UK, with repeated i. m. injections of the antigen or placebo. The main result was the demonstration of a predetermined antibody response in about 25% of patients (Wilkinson et al. 2005). Side effects were mainly local inflammatory reactions and a single occorence of neurological worsening, later identified at autopsy as due to a new type of inflammatory meningoencephalitis (Nicoll et al. 2003).

Lastly – so far – a phase 2b trial recruited 375 patients, to be given repeated i. m. injections of either the Elan amyloid antigen (AN1792) or matched placebo. The injections were discontinued, after 2 injections in most cases, because of the occurence of several cases of subacute meningoencephalitis (SAME) of presumed auto-immune origin: in total 18 (6%) of patients developed a syndrome of SAME, severe in 6, followed by death in 2 or a bedridden state in 1 (Orgogozo et al. 2003).

Despite the truncated antigen administration the predetermined antibody respose was achieved in 20% of the exposed patients (none under placebo), without correlation with the occurrence of SAME. Neither the main clinical outcomes (ADAS-cog, MMSE, CDR ...) nor the total brain volume at MRI showed aparent benefit, in total and in the antibody responders (Gilman et al. 2005; Fox et al. 2005). However a positive response was objectived with an ad hoc neuropsychological test battery, correlated with the antibody response and with changes in the A-beta/tau ratios in the CSF towards more normal values (Gilman et al. 2005).

In the few patients from this trial who went to autopsy, with or without SAME, a consistent reduction of the expected amyloid deposits with some evidence of amyloid removal was observed (Ferrer et al. 2004).

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