

Main Topics

Postacute stroke treatment

MT-1

The role of growth factors for functional recovery after ischemic stroke

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Mechanisms by which the damaged brain might recover from stroke include neural rewiring and endogenous progenitor (stem) cell proliferation in brain. Polypeptide growth factors stimulate these processes and may be useful as treatments to enhance neurological recovery after stroke. For example, in preclinical studies, we have shown that exogenously administered basic fibroblast growth factor (bFGF) stimulates sprouting from undamaged neurons and stimulates endogenous progenitor cell proliferation in the rat brain following focal cerebral infarction. These effects are paralleled by an enhancement of recovery of sensorimotor function of the contralateral limbs. Recent data have been obtained using a covalently dimerized bFGF (dFGF), which appears to be more stable and potent than the monomer. Growth factors may represent treatments that can be administered subacutely (days or weeks) following stroke in order to enhance neurological recovery.

MT-2

“Forced use” versus conventional physiotherapy for post-stroke motor deficit

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It has been claimed that Constrained Induced (CI; Forced Use) Movement Therapy has a large and clinically relevant impact on the recovery of upper extremity function in the chronic and acute phase post stroke. Its effectiveness appears to be related to successfully treating learned non-use by directing the patient's attention to the paretic arm with a high intensity of upper extremity function training. This study presents the findings of a critical review and meta-analysis of 10 studies (4 true-, 1 quasi-, and 5 pre-experiments) evaluating the effects of CI therapy. The four randomised controlled trials (RCTs) included between-group designs, and the quasi-experiment was a controlled single case study. In three RCTs statistics were applied, demonstrating a significant reduction of limitations in upper extremity function as a result of CI-therapy. With the exception of one RCT (N=66), all studies included a small sample size (range N=1 to N=23), reducing statistical power. Remarkable was the variety in amount of CI-therapy applied between the experimental condition and the control condition in the different studies (range 0 to 84 hours). In two RCTs control was attempted for non-specific parts of CI therapy. The methodological quality of the studies varied from poor to moderate. Combining the individual effect sizes of three RCTs revealed a significant moderate

summary effect size for functional recovery of upper extremity function. In one RCT the effects of CI-therapy were clinically relevant in patients with sensory disorders and hemi-neglect. Future research should investigate whether directing attention and/or intensity of CI therapy are the effective components.

MT-3

Imaging correlates for strategies to improve functional restoration after stroke

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The mechanisms that are responsible for the remarkable potential for functional recovery from stroke remain unclear, and functional neuroimaging modalities increasingly are being used to investigate this issue. Such studies confirmed that recovery of function is related to the volume of penumbra tissue that escaped infarction and can be reintegrated into the functional network. For language, reactivation of primary functional areas in the dominant hemisphere is associated with the best prognosis. Evidence for functional plasticity in the immediate vicinity of infarcts, as demonstrated under experimental conditions and explained by increase in functional areas due to decreased collateral inhibition is still limited after stroke in humans. Often, functional changes in the large-scale networks that support motor and language functions have been found. A frequent finding is an increase in cerebral blood flow response in corresponding regions of the healthy hemisphere during unilateral motor or speech activation. This phenomenon might reflect transcallosal disinhibition of usually suppressed contralateral activity; however, it is not yet clear whether that is related to functional recovery, and there are several observations indicating that it is often inefficient. Ipsilateral reactivation of eloquent areas in the functional network – e.g. of temporal regions in patients with post-stroke aphasia – was usually related with more efficient recovery than activation of corresponding contralateral regions, and was also observed in patients benefiting from drug treatment adjuvant to speech therapy.

MT-4

Evidence-based stroke rehabilitation

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Most of the current practice in neurorehabilitation (NR) is not evidence-based. This is surprising considering the substantial amount of health expenditure going into post stroke care. Today, early NR should be performed within the setting of a comprehensive stroke unit (SU) (level 1 evidence and grade A recommendation). SUs that include comprehensive care, interdisciplinary organization, staff conferences at least at weekly intervals, staff training, and early involvement of spouses and caregivers in the NR programme seem to function best. The efficacy of such care is substantial and has been shown to be beneficial over several years when compared to treatment and rehabilita-

tion received within general medical wards. Other measures mostly are based on level C evidence or rely on published expert opinions and national guidelines. Accordingly, the time frames for NR interventions as for the initiation, intensity and duration are less well proven. The time that elapses after a stroke before the NR programme starts should probably be less than 3 weeks and the intensity for NR therapy sessions should not be under 3 hours daily for most patients. In addition, some general aspects of NR are very powerful predictors and include environmental stimulation, emotional support, as well as empowerment strategies. Positive environmental stimuli have experimentally been shown to support adult neurogenesis as well as restoration of sensorimotor function following focal brain lesions. Measures of empowerment include domains such as self-esteem and self-efficacy, autonomy in social and community relations, and feeling of control for the future. These measures correlate with quality of life and can be of additional use for measuring NR outcome.

Distal myopathies

MT-5

Distal myopathies: differential diagnosis

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The distal myopathies (DM) are a heterogeneous group of disorders identified by primary involvement of hands or feet and by myopathic features in the muscle biopsy. They have been classified following a series of clinical criteria such as the initially affected distal muscle groups and age of onset, the pattern of inheritance and the histopathological characteristics in the muscle biopsy. These primary DM include: 1) Late adult onset Type 1 or *Welander myopathy*, 2) Late adult onset Type 2 or *Markesbery-Griggs/Udd myopathy*, 3) Early adult onset Type 1 or *Nonaka myopathy*, an autosomal recessive disease indistinguishable from *hereditary IBM*, 4) Early adult onset type 2 or *Miyoshi myopathy*, with autosomal recessive and 5) Early adult onset type 3 or autosomal dominant *Laing myopathy*.

To properly identify these different myopathies and to differentiate them from other neuromuscular diseases it is crucial to determine the phenotype by a careful neurological examination. The EMG examination is very important to differentiate a neurogenic process, like the distal spinal muscular atrophy among others, and also to distinguish some myopathies with distal involvement such as the Steinert myotonic dystrophy. The muscle biopsy is a key tool to study the presence of vacuoles, a finding common to many of these distal myopathies and to discard some metabolic myopathies (Debrancher deficiency, acid maltase deficiency, phosphorylase b kinase deficiency, lipid storage myopathy) or congenital myopathies (Nemaline myopathy, central core or centronuclear myopathies) or the desmin/Myofibrillary myopathies that may start with a distal involvement. Finally the genetic studies are or will soon be the final clue to understand these myopathies at a molecular level. At present, it is known that mutations in the dysferlin gene cause the

Miyoshi myopathy phenotype of DM as well as another identified phenotype, the DAT (distal anterior phenotype) and a proximal phenotype of muscular dystrophy (LGMD2B). On the other hand, Welander distal myopathy was linked to chromosome 2p12 in 1999, but the gene has not been identified. Further, Nonaka myopathy previously linked to chromosome 9p1-q1 is now known to be caused by mutations in the UDP-N-acetylglucosamine-2-epimerase/N-acetylmannosamine kinase gene (GNE), as in autosomal recessive inclusion body myopathy (IBM2). The tibial muscular dystrophy has been linked to 2q31, and findings in the muscle biopsy suggest that titin may be the gene responsible for this myopathy.

Finally, the gene corresponding to Laing myopathy, although linked to chromosome 14, has not been described yet.

MT-6

Tibial muscular dystrophy and related distal myopathies

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Tibial muscular dystrophy (TMD) is dominant late-onset distal myopathy, relatively common in Finland with a prevalence above 6/10⁵. One TMD family has been reported from northern France, one from Belgium and a similar late-onset distal myopathy family (LODM, Markesbery-Griggs disease) from the USA. Linkage to chromosome 2q31 was established in all of them. TMD patients have late-onset difficulty walking on heels and slowly progressive foot drop, whereas some rare Finnish patients homozygous for the common Finnish TMD haplotype develop a severe childhood onset LGMD phenotype. The positional and functional candidate gene for TMD was the giant sarcomeric protein titin, which interacts with muscle specific Ca²⁺-activated neutral protease calpain3. Previous immunohistochemical and Western blot studies with titin and calpain3 antibodies have shown secondary decreased amount of calpain3. A major sequencing effort of the giant *titin* gene revealed a highly interesting mutation including 11 bp, changing four amino acid residues in the last Mex6 exon in the Finnish TMD patients. In the French TMD family, a Leu>Pro mutation in Mex6 position 293,357 was discovered. Mex6 is adjacent to the known calpain3 binding site Mex5 of M-line titin. Immunohistochemical analysis using the M-line titin antibody M8/9 showed loss of epitope recognition in TMD muscle samples, further emphasizing the functional defect caused by the mutation and in agreement with the previous results of secondary calpain3 defect in TMD. These are the first mutations in titin to cause human myopathy. TMD is a titinopathy with direct genetic testing available for the known mutations. The use of genetic testing has considerably expanded the phenotype of TMD.

MT-7

Dysferlin myopathies – the distal and proximal phenotypes.

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The initial localisation of the gene for a form of limb-girdle muscular dystrophy and Miyoshi myopathy to the same region of chromosome 2p13 in 1994 and 1995 respectively first raised the possibility that these two apparently distinct disorders might be allelic. This was subsequently confirmed by the cloning of the dysferlin gene in 1998, and the recognition that even identical homozygous mutations in this gene could give rise to different phenotypes in the same family. Classically, the distal presentation seen in dysferlinopathy involves the gastrocnemius

muscle predominantly, though a tibial anterior predilection has also been described. The proximal phenotype can be associated with distal involvement which is apparent on imaging but not clinically obvious. Upper limb involvement is not usually prominent at onset, though an early and very focal wasting of the biceps muscle is typically seen. Patients with either distal or proximal presentation usually develop symptoms in their late teens or early twenties with good muscle prowess before. Progression is typically relatively slow, though more rapid progression has also been described. The diagnosis can be confirmed by protein and DNA analysis.

Dysferlinopathy was an early and graphic example in the muscular dystrophy field of clinical heterogeneity in association with a single gene defect, and provides a model for studying the variability of muscle involvement which is now recognised to be a much more widespread phenomenon than had previously been thought.

CNS infections

MT-8

Bacterial infectious diseases of the nervous system, old problems and new therapeutic solutions

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A major cause of mortality and sequelae in bacterial meningitis are cerebral complications arising during the acute phase of the disease such as brain oedema, cerebrovascular arterial and venous involvement, or hydrocephalus resulting in an increased intracranial pressure (ICP).

Cerebrovascular involvement is usually detected by CT or MRI (including diffusion weighted imaging) and MR angiography. Transcranial Doppler sonography may be useful in diagnosing and monitoring the involvement of great arteries at the base of the brain during the acute phase of bacterial meningitis. High-resolution MRI can visualize and differentiate the sites of auditory and vestibular involvement in adult patients with hearing loss as a complication of bacterial meningitis.

In combination with antibiotics, adjunctive therapeutic approaches include treatment of increased ICP (e.g. administration of mannitol, hyperventilation, or external ventricular drainage in case of hydrocephalus), septic sinus venous thrombosis (using heparin), epileptic seizures and the correction of electrolyte disturbances.

A recent meta-analysis showed that dexamethasone reduced severe hearing loss overall in *Haemophilus influenzae*-meningitis in children. In pneumococcal meningitis, only studies in which dexamethasone was given early suggested protection, which was significant for severe hearing loss and approached significance for any neurological or hearing deficit. Aside from dexamethasone, several therapeutic agents that may limit meningeal inflammation have shown beneficial effects in animal models of meningitis, e.g., antioxidants and inhibitors of matrix metalloproteinases, caspases, and poly(ADP)ribose polymerase.

MT-9

The immunobiology of prion diseases

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Mice deficient in the normal prion protein are resistant to exposure to prion infectivity, and expression of the normal prion protein by neurons is necessary for the development of histological damage¹. But how do prions reach the brain after entering the body from peripheral sites? The first portal of entry in the gut may be represented by M-cells². Neuroinvasion, i.e. the process by which prions march through the body of the host towards the brain, is dependent upon expression of the normal prion protein in a non-hematopoietic extracerebral site³. We therefore developed the hypothesis that neuroinvasion takes place in two distinct steps: first the lymphoreticular system is diffusely colonized by the agent, while at a later time infectivity progresses from lymphoreticular organs to the central nervous system⁴, probably via sympathetic nerves^{5,6}. There is an absolute requirement for B-lymphocytes in peripheral prion pathogenesis⁷. Surprisingly, the presence of the normal prion protein is not necessary on B-lymphocytes to enable them to support this process⁸. The mechanism of action of B lymphocytes may consist of presentation of lymphotoxin-β to follicular dendritic cells⁹. This paves the way to post-exposure prophylaxis strategies¹⁰ that exploit the anti-prion effect of soluble lymphotoxin-β receptors. Why do follicular dendritic cells accumulate prions? We tested the hypothesis that prion uptake may be complement-mediated. Indeed, certain components of the complement system (C1q, CR1/2) proved to play an important role in pathogenesis¹¹. Finally, we have found that transgenic expression of an anti-PrP antibody heavy chain suffices to confer to mice antiprion protection – a finding that may be relevant to the development of antiprion vaccines¹².

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MT-10

Diagnostic and therapeutic challenges of CNS parasitoses

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Protozoa, helminths and even arthropods may cause acute or chronic inflammation of the central nervous system through various pathophysiologic mechanisms.

They involve direct infection or infestation, respectively, of both central nervous tissue and meninges as well as intracranial blood vessels leading to acute or chronic meningitis, meningoencephalitis, meningovascularitis or myelitis, but also space occupying cysts and granulomata, as well as indirect mechanisms, either of immunologic, toxic or hypoxic nature.

Most parasitic diseases of the nervous system are seen in patients coming from tropical or subtropical areas (tourists, refugees etc.) or in the immunocompromised (e.g. HIV) patient. Those parasitic diseases acquired in central Europe, e.g. *Toxocara canis*, *Trichinella spiralis* spp or free-living amoebae infections are seen extremely rarely. These two aspects, the rarity of locally acquired parasitic infections/infestations as well as the non-familiarity of European medical doctors with imported CNS parasitoses render them to diseases with high morbidity and mortality. Timely diagnosis and appropriate antimicrobial and adjunctive chemotherapies constitute those diagnostic and therapeutic strategies which minimise the challenge of these CNS diseases. Problems in appropriate history taking (exposition, travel anamnesis etc), diagnostic procedures far beyond the scope of what is regularly employed in CNS or PNS diseases, laboratory results which are difficult to interpret (peripheral or CSF eosinophilic pleocytosis or the absence of it, etc.), specific diagnostic challenges like the interpretation of serology, granulomatous or cystic findings in neuroimaging, all contribute to many difficulties and delays. Furthermore, diagnostic procedures beyond the central nervous system require an interdisciplinary approach to patients with suspected CNS parasitoses. Since, however, some of these diseases (e.g. cerebral malaria, acute amoebic-meningoencephalitis, CNS babesiosis, encephalitis caused by *Trypanosoma brucei rhodesiense*, Trichinosis of the CNS, eosinophilic encephalitis/myelitis due to *Gnathostoma spinigerum* etc.) do not allow time consuming procedures (loss of time contributing to high morbidity and mortality) quickest possible diagnoses and induction of appropriate antimicrobial chemotherapies and adjunctive therapeutic measures are warranted. Beside these extremely important aspects, this lecture will concentrate on the top 3 CNS-parasitoses imported to

Europe in the immuno-competent patient, i. e. cerebral malaria, African trypanosomiasis (sleeping sickness) and neurocysticercosis.

In cerebral malaria (the signs and symptoms of CNS involvement are caused by hypoxia and intraparenchymatous haemorrhages) the diagnostic golden standard still is the visualisation of asexual *Plasmodium falciparum* stages in the peripheral blood. The therapy of a patient with cerebral malaria must concentrate both on schizontocidal chemotherapy (beside Quinine, new drugs like Artemeter derivatives as well as orally administrable combination drugs like Atovaquone/Proguanil) and on adjunctive therapeutic strategies (early intensive care, whole-blood exchange etc.). The management of East African Trypanosomiasis includes the diagnostic challenge of the visualisation of *Trypanosoma* spp. in the peripheral blood and, in particular, in the CSF. Sleeping sickness (= trypanosomal meningoencephalitis) is treated with a highly toxic arsenical (Melarsoprol) or the modern drug of Eflornithin the production of which has been recently suspended. The diagnostic challenges of neurocysticercosis concern, in particular, the neuroimaging techniques as well as the interpretation of serologic results in CSF and serum. Neurocysticercosis is treated with Praziquantel or Albendazole respectively. The adjunctive therapy of a patient with neurocysticercosis may comprise neurosurgical intervention and must comprise high dose steroids as well as – in some instances – anticonvulsive drugs.

In a final summarizing slide those protozoal and helminthic diseases which may be seen in rare instances in European patients are presented with respect to diagnostic procedures and best possible therapies.

Recent advances in movement disorders

MT-11

Pathophysiology and pharmacology of L-dopa-induced dyskinesias

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Long-term dopamine replacement therapy for Parkinson's disease, especially that based upon levodopa, is associated with the appearance of debilitating involuntary movements, levodopa-induced dyskinesia. The understanding of abnormalities in the circuitry within the basal ganglia in levodopa-induced dyskinesia has advanced considerably in the last decade. Patterns of neural activity throughout the basal ganglia are disrupted in levodopa-induced dyskinesia, but in particular the direct striatal output pathway becomes overactive and the outputs of the basal ganglia become grossly underactive. This understanding, while not complete and certainly simplistic, has been successfully employed to define novel therapeutic approaches to levodopa-induced dyskinesia. On the one hand, such novel approaches can reduce the development of dyskinesia when an anti-parkinsonian treatment, other than levodopa monotherapy, is given *de novo*. On the other hand, it is now possible to define adjunctive therapies to dopamine replacement that can enable the continued use, in patients with established dyskinesia, of levodopa to alleviate parkinsonism while reducing dyskinesia.

An appreciation of the role of the direct striatal output pathway in the development of levodopa-induced dyskinesia has identified means of

1) treating parkinsonism *de novo* in a way that may be associated with a lower incidence of dyskinesia than levodopa monotherapy e.g. D2 selective agonists, A2a adenosine antagonists, combination of NDMA antagonists with levodopa.

2) Using an adjunctive therapy alongside dopamine replacement therapy to reduce established dyskinesia e.g. alpha-adrenergic receptor agonists, cannabinoid receptor antagonists, NMDA and metabotropic glutamate receptor antagonists, histamine H3 agonists, mu opioid receptor antagonists.

MT-12

Multiple system atrophy

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First described in 1969 by Graham and Oppenheimer, multiple system atrophy (MSA) is increasingly recognized as distinctive neurodegenerative disease. Clinically, it is characterized by autonomic failure, parkinsonism, cerebellar ataxia and pyramidal signs in any combination. The motor disorder is dominated by parkinsonism in 80% of the patients (MSA-P) or by cerebellar ataxia in the remaining 20% (MSA-C). Although the clinical syndrome is often highly characteristic in advanced stages clinicopathological and epidemiological data indicate that MSA is underdiagnosed in movement disorders clinics as well as in the general population. It remains to be determined whether the recent consensus diagnostic criteria for MSA (Gilman et al. 1998) will improve patient recognition. Physical manoeuvres and/or drug therapy may considerably improve orthostatic dysfunction and urogenital complaints, however, in practice these measures are not always implemented. The motor disorder of MSA cannot be treated effectively in most patients although transient relief may be obtained by L-Dopa. Latter should therefore be administered to all MSA patients with parkinsonian features. The recent discovery of characteristic oligodendroglial and neuronal alpha-synuclein inclusions in MSA brains has greatly stimulated research into the pathogenesis of this disorder. This work will hopefully result in novel neuroprotective treatment strategies. Neuroregenerative approaches such as embryonic cell grafting are already being explored experimentally in animal models and may become available to restore lost circuitry and to improve function in MSA patients.

MT-13

Inappropriate daytime somnolence and anti-parkinsonian medications

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A growing body of evidence demonstrate that dopaminergic systems play a greater role than formally recognised in the control of sleep and wakefulness mechanisms. Recent reports of "sleep attacks" in patients with Parkinson's disease (PD) largely contributed to highlight this topic.

The aetiology of sleep and vigilance problems in PD is multifactorial, the disease being a major confounding factor to study the direct effects of antiparkinsonian drugs on vigilance. Before 2000, the majority of available data was restricted to few clinical reports on L-dopa, with conflicting findings on night sleep quality.

In spite of a growing interest, clinical studies considering sleep and vigilance symptoms as primary outcomes remain limited. Phase I trials in healthy volunteers show that most dopaminomimetic agents induce sedation. The analysis of placebo-con-

trolled trials conducted in PD confirms that somnolence is observed with any dopaminergic medication.

"Sleep attacks" have been first described on some dopamine agonists. It remains to be demonstrated if such episodes are a distinct entity or an extreme form of inappropriate daytime somnolence. "Sleep attacks" have now been described in post-marketing surveillance with most antiparkinsonian medications, including L-dopa monotherapy. Pharmacoepidemiological surveys have confirmed that such episodes are not restricted to some agonists, but are observed with any antiparkinsonian dopaminergic treatment.

In summary, a growing body of evidence shows that sedation is a true pharmacodynamic dopaminergic property, and that doctors and patients should consider this sedative effect when prescribing and consuming antiparkinsonian medications.

Disease progression in multiple sclerosis

MT-14

Pathology and MS progression

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Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system leading to the formation of demyelinated plaques in the brain, cerebellum, brain stem and spinal cord. The main pathological characteristics are inflammatory infiltrates consisting of T cells, plasma cells and macrophages/microglia, demyelination, axon loss and gliosis. Recent detailed studies revealed different patterns of oligodendrocyte pathology within the lesions with one type of lesions characterized by extensive recruitment of progenitor cells and subsequent remyelination and the other type showing pronounced loss of oligodendrocytes, failure of progenitor recruitment and absence of remyelination. Subsequently, four different immunopathological subtypes of lesion pathogenesis were defined. Clinically, MS is characterized by a highly variable disease course, starting in the majority of cases with a relapsing-remitting course with a transition to secondary progression in the later disease stages. A minor proportion of MS cases start with a primary progressive disease. The exact pathological basis of the different disease courses has not yet been defined. However, there are recent data suggesting that in secondary progressive MS compared to relapsing-remitting MS, there is a greater accumulation of axon damage and a failure of remyelination. In primary progressive MS, inflammation is less severe and oligodendrocyte loss is more pronounced than in the other disease courses. These data suggest that there may be quantitative as well as qualitative differences between the disease courses leading to the progression of MS pathology.

MT-15

MRI and MS progression

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In the last 15 years, MR imaging and spectroscopy have allowed an in vivo assessment of the evolving pathology in multiple sclerosis. The sensitivity of MRI has provided new understandings of pathogenic mechanisms, and a tool with which to

monitor treatments. In addition, early MRI findings are of great value in diagnosis, and also provide important prognostic information.

In understanding the course of MS, the main observations are:

1. Focal demyelination is normally associated with an initial phase of blood brain barrier breakdown and inflammation.
2. Axonal damage and loss occurs in lesions and normal appearing tissues and becomes increasingly marked with progressive disability.
3. Axonal loss is partly related to inflammation and partly independent.
4. Progressive abnormality occurs in the normal appearing white matter which precedes focal lesions and may be associated with progressive disability.
5. Brain plasticity occurs in response to MS pathology.

There are important unresolved questions. One is the extent to which early inflammation and its suppression modulate the long-term prognosis for disability and axonal loss. Serial studies from clinical onset using multiple MR techniques are required. Other areas where new MR developments may assist are in monitoring remyelination, and the development of cell specific imaging.

MT-16

Immunology and MS progression

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A characteristic feature of multiple sclerosis (MS) is the development over time of a progressive chronic disease course in a large segment of the patient population. Although initially it was thought that this reflected the loss of oligodendrocytes with the capacity to effect remyelination from the lesion, more recent studies have shown that chronic impairment correlates more closely with loss of axons. Furthermore, it has been shown that proliferating premyelinating oligodendrocytes are present at the edge of active lesion, suggesting that additional unknown mechanism prevent remyelination in MS. This has led to the suggestion that the re-expression of recently discovered new families of developmentally regulated receptor/ligands that inhibit oligodendrocyte differentiation during development may prevent remyelination in the MS lesion. The formation of an astrocytic scar may also serve to limit the remyelinating activity of the lesion. From an immunological perspective, the development of chronic disease may also reflect the acquisition of an immune response to additional target antigens that are exposed within the injured CNS, a phenomenon known as epitope spreading. Although initial studies indicated that autoreactive T-lymphocytes can be derived from MS patients' blood and cerebrospinal fluid (CSF), subsequent data showed that myelin-antigen-reactive T-lymphocytes are also present in the blood of most normal individuals. Thus, the development and persistence of MS might depend not only on the generation of self-reactive T-cells, but also on the presence or absence of the appropriate number of functional regulatory cells. There is now compelling evidence that T-cells that specialize in the suppression of an immune response play a critical role in immune regulation. These data suggest that an intrinsic fault in molecular control mechanisms may play a pivotal role in contributing to the persistence of autoimmune responses in MS.

MT-17

Clinical aspects and MS progression

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The last fifteen years have witnessed remarkable advances in the understanding of multiple sclerosis (MS). Probably the most significant of these advances have been the new insights into the clinical course of the illness. First, largely because of the application of MRI to the study of MS, the active and progressive nature of the disease in most patients even during the early relapsing remitting phase became evident. Since partially effective treatments are now available, the appreciation of the active nature of the illness even during periods of clinical stability has had profound implications of the treatment of the disease. Second, at the other end of the spectrum, evidence has accumulated indicating that the insidious progression often seen in the secondary progressive stage of the illness may be independent of the acute inflammatory processes associated with acute worsening. A clear understanding of the relative importance of inflammatory and degenerative processes in the progression of clinical disability is essential with respect to both the optimal care of patients and for the design and testing of new therapies. Despite some new approaches to the assessment of clinical disability, clinical measures of progression are insensitive and unable to provide insights into the underlying disease mechanisms contributing to progression. Using data derived from two phase III clinical trials of a beta interferon in patients with secondary progressive disease, differences in the extent of progression and response to a therapy that targets the acute inflammatory component of the illness demonstrates the limitations of clinical measures of progression. Necessary are imaging and biological markers that will provide a better understanding of the role of various elements of the MS lesion including immune processes, irreversible myelin loss, axonal damage, and gliosis in progression of disability in MS.

Glioma: from molecule to treatment

MT-18

Molecular correlates of tumour progression

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Astrocytic tumours have been known to progress with time to more malignant tumour forms for over a century. We have been studying a series of 190 astrocytic gliomas (136 glioblastomas (GB), 39 anaplastic astrocytomas (AA) and 15 astrocytomas (A)) for abnormalities of genes in the RB1 pathway (*CDKN2A*, *CDKN2B*, *CDK4* and *RB1*), the p53 pathway (*p14^{ARF}*, *MDM2*, and *TP53*), as well as *PTEN* and *EGFR*. A and AA had no wild-type *TP53* or one mutated allele in 67% of cases. Only 29% of the GB had no wild type *TP53* with an additional 6% having one mutated allele. Wild type *p14^{ARF}* was absent from 38% of GB and a further 8% had amplification and overexpression of *MDM2*. Thus 76% of GB (103/136), 72% of AA (28/39) and 67% of A (10/15) had a deregulated p53 pathway indicating that this is almost a prerequisite for astrocytic tumours. In comparison all A had at least one wild type *RB1* gene and no other abnormalities of this pathway. Abnormalities of the RB1 pathway occurred in 21% AA and 67% GB either by mutation/homozygous deletion of *RB1*, *CDKN2A* and *CDKN2B*, or

amplification of *CDK4*. This indicates that disruption of the RB1 pathway is directly related to astrocytic tumour progression. Amplification of the *EGFR* gene was not observed in A, was unusual in AA (8%) but common in GB (33%). Loss of wild type *PTEN* occurred in one AA (3%) but was very common in GB (47%) and could be found together with all combinations of the other genetic abnormalities. Molecular diagnosis as well as molecular therapeutic approaches must consider the various ways cellular mechanisms are disrupted.

MT-19

Novel drugs and techniques to overcome chemoresistance in malignant gliomas

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The standard treatment for glioblastoma includes cytoreductive surgery and postoperative involved-field radiotherapy. The role of chemotherapy is less well defined. Among numerous novel cancer chemotherapy drugs evaluated in recent years, only the alkylating agent temozolomide has gained a place in the treatment of recurrent glioblastoma, with the results for first-line therapy (EORTC trial 26981) being available soon. Efforts to enhance the effects of temozolomide include the use of O⁶-benzylguanine, an inhibitor of the enzyme O⁶-alkylguanine DNA alkyltransferase, which repairs temozolomide-induced DNA damage. Although preclinical data supported this approach, clinical data on the efficacy and tolerability of combining temozolomide with OGAT inhibitors have not been made available. Since many glioblastomas overexpress the epidermal growth factor receptor (EGFR), novel agents targeting EGFR or EGFR-dependent signal transduction may also assume a role in the pharmacotherapy of malignant gliomas. The overall resistance of glioblastomas to chemotherapy is not only due to poor drug delivery, but also to molecular abnormalities favouring resistance to apoptosis. For instance, glioblastoma cells express high levels of various antiapoptotic proteins, notably of the BCL and XIAP families. Resistance mediated by these proteins could possibly be overcome by the use of small peptides mimicking the action of natural XIAP antagonists, e.g., Smac/DIABLO. Further, glioblastomas do not respond with apoptosis to genotoxic stress even though most tumours p53 wild-type status. Gene transfer strategies using p53-based synthetic genes such as CTS-1 or small molecules such as CP-31398 may help to overcome this hitherto poorly defined pathway of resistance to chemotherapy.

MT-20

Oligodendroglioma: a treatable tumour

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Oligodendroglial tumours (oligodendrogliomas and oligoastrocytomas) are uncommon primary brain tumours, but in recent years they have been increasingly recognized by the pathologists among all gliomas. Low grade (grade II WHO) oligodendroglial tumours display more often an indolent course allowing most patients to survive for many years after diagnosis, whereas high grade (grade III WHO) tumours have a more aggressive behaviour. Overall the prognosis of oligodendroglial tumours is better than the astrocytic counterparts. Surgical resection, when feasible, represents the first therapeutic approach, even if there is uncertainty regarding the prognostic significance of the extent of resection. Early radiation therapy does not seem to

impact the survival of patients with incompletely resected low grade oligodendroglial tumours, whereas it is the standard adjuvant treatment in the anaplastic forms. In recent years the susceptibility of “aggressive” (symptomatic, enhancing, but grade II) and anaplastic oligodendrogliomas and oligoastrocytomas (grade III) to cytotoxic chemotherapy has been recognized to be unique among gliomas. Both recurrent and newly diagnosed tumours respond predictably (70–90% complete and partial responses) to alkylating agents (especially the PCV regimen). In this regard trials are ongoing, looking at the value of adjuvant or neoadjuvant chemotherapy after surgery. High dose chemotherapy with stem cell rescue and novel drugs such as temozolomide are being investigated. Some molecular alterations (loss of heterozygosity of chromosome 1p and 19q) correlate with the response to chemotherapy and probably in the near future will allow the identification of subgroups of patients to be treated upfront by chemotherapy.

The role of continuous low dose drug exposure in low grade oligodendroglial tumours will be soon investigated.

Up to date median survival after multimodality treatment ranges between 4–5 years for anaplastic tumours and 9–10 years for low grade tumours.

Basic mechanisms of epilepsy

MT-21

Mechanisms of genetic epilepsies

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Epileptic discharges are associated with excessively synchronous and (usually) excessively intense neuronal discharges that arise without obvious precipitating factors. Experimental models have told us much on how such discharges can start. In the case of focal epilepsies, interconnections between excitatory neurons provide the substrate. These connections need to be sufficiently dense and strong, and the population needs to be sufficiently large, for activity to recruit enough neurons to sustain the epileptic discharge (1). The “intrinsic” electrical properties of the excitatory neurons can result in burst firing, which amplifies their synaptic outputs, which in turn can play a key role in promoting epileptic activity. The connections between the excitatory neurons are necessary for normal function, and excessive recruitment of these neurons is normally controlled by inhibitory interneurons that normally damp down excitation before it gets out of hand. Primary generalised absence seizures differ markedly from focal seizures, in requiring the interaction of thalamus and cortex, and in the marked involvement of inhibitory synapses in the synchronisation of the spike and wave discharge generated by the cortex (2).

Recent advances in the genetics of epilepsy have revealed several mutations with physiological consequences directly relevant to the processes I have just outlined (3). For instance, Generalised Epilepsy with Febrile Seizures + can be caused by two quite different kinds of mutations. One is of the inhibitory GABA receptor, weakening its response to GABA (and hence impairing the controlling function of inhibitory neurons), while the other is of sodium channels, resulting in a prolongation of the action potential (most likely resulting in strengthened excitatory transmission). Mutations of GABA receptors that attenuate the response to benzodiazepines have been linked with both absence seizures and to febrile seizures. Specific mutations of

potassium channels and nicotinic cholinergic receptors have been linked with other kinds of epilepsy.

These cases are very exciting, but they do represent a minority of epilepsies. The functional significance of other epilepsy-related mutations remains obscure, as does their relationship with our current understanding of epileptogenesis. Even where we have a clear cellular phenotype that appears to be pro-epileptic, much work remains to link the genetic mutation to the system level disruption responsible for the seizures.

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MT-22

Anticipation of epileptic seizures

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For a vast majority of epileptic patients, seizures occur suddenly in the absence of identifiable external precipitants. The unpredictability of seizure onset represents a major threat for persons with epilepsy and a cause of disability¹ and mortality. Prediction of seizure onset, even of short term, would provide time for the application of preventive measures to minimize seizure risk and, ultimately, improve quality of life.

Intracranial recordings, realized in specific patients candidate for surgical treatment, offer the most precise access to the emergence of a seizure. Ways to anticipate seizure onset before the first intracranial electrical changes have been intensively investigated using conventional linear (i.e. frequency) analyses. Nevertheless, the prediction does not exceed more than a few seconds before visual detection of the seizure. Non-linear analysis offers an alternative way to characterize qualitative changes in the dynamics of complex systems and promises to be important for clinical practice. Applied to intracranial recordings of patients with temporal lobe epilepsy these methods have shown that the evolution toward a seizure involves not just two states – interictal and ictal – but also a *pre-ictal* transitional phase of several minutes that is not detected by linear methods. Similar strategies have been also applied to neocortical seizures, and to non-invasive, scalp EEG recordings. The neurobiological bases of this pre-ictal phase are largely unknown, but the study of changes in synchronies may give some clues. A sufficient level of sensitivity and specificity should be reached before contemplating clinical applications.

MT-23

Mechanisms of drug resistance and their relevance to epilepsy

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Long-term clinical experience with epilepsy has shown that approximately 80% of patients can become seizure-free. The other 20% of patients continue to have incapacitating seizures despite treatment with maximal dosages and optimum serum levels of more than one drug. The mechanisms underlying such pharmacoresistance to anti-epileptic drugs are not well understood. It is likely that they will include both pharmacodynamic and pharmacokinetic mechanisms. There is increasing interest in the latter mechanism(s), in particular on the role of drug transporters, i.e. membrane transport pumps responsible for passage of drug into and out of the cell.

There is now increasing evidence to show that transport pumps such as P-glycoprotein (Pgp) and Multi-drug resistance protein 1 (MRP1) are over-expressed in brain tissue removed during epilepsy surgery. However, although providing some evidence of possible mechanisms, it does not prove that these transport proteins subserve drug resistance. Specifically it is important to show that over-expression is pathogenic rather than an epiphenomenon. This will require elucidation of all the different types of transporter proteins expressed in the CNS, whether their expression is increased in epileptic foci, whether they act as transporters for the different antiepileptic compounds, and whether genetically determined variation in expression of these transporters predisposes to the development of epilepsy resistance. Lastly, clinical studies designed to modulate the function of these transporters and whether this has an effect on seizure control will also be needed. The talk will focus on these aspects and will review the latest research evidence.

Early cognitive changes and differential diagnosis in dementia

MT-24

Mild cognitive impairment – concept and limitations

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The concept of MCI has been introduced to fill the gap between two discrete cognitive states: that associated with aging and that which characterizes dementia. The concept offers two main advantages. First, it provides a diagnostic entity for a large proportion of patients consulting memory clinics that do not reach the threshold of dementia. Second, it allows one to shift attention toward the early stages of diseases where treatment might be more efficient and useful. On the other hand, ambiguity clouds the current conceptions of the content and scope that MCI is thought to cover:

- At first glance, MCI covers several different pathological entities, even though the precise nature of these entities remains unclear. This heterogeneity among the diseases responsible for MCI may hamper the choice of diagnostic criteria (memory impairment alone or cognitive changes as well), the knowledge of evolution (some patients aggravate whereas others are stable or even improved!), and the therapeutic approaches (symptomatic or disease related?).
- In fact, MCI is considered more and more as a diagnostic category for prodromal AD. Two arguments support this interpretation: 1) the choice of memory impairment as the main criterion for MCI; 2) the fact that up to 80% of subjects with MCI will convert to AD in approximately 6 years. If so, the question is to know whether it is possible today to recognize

the disease in its prodromal phase. Unfortunately, there is no biological marker for AD that can reliably identify the disease. Brain imaging may be more useful, but its real value at this stage remains to be established. Specific memory tests are the most helpful because the pattern of memory deficits of patients with prodromal AD has been clearly defined. To conclude, the main issue is to define what is useful for a given individual. Is it to diagnose MCI, a syndrome of unknown aetiology, or to detect the disease that is responsible for most of the cases, i.e. incipient AD? The question is opened.

MT-25

The role of neuroimaging in mild cognitive impairment and early dementia

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Mild cognitive impairment (MCI) is a clinical syndrome to describe patients with discrete cognitive deficits insufficient to fulfil the criteria for Dementia. The majority are characterised by memory impairment, commonly referred to as MCI of the amnesic type. Most of these cases are believed to represent early Alzheimer's disease and progress to fulfil the criteria of Dementia at an annual rate of 15%. This group shows hippocampal atrophy, which is a valuable predictor of subsequent deterioration. However, MCI is heterogeneous and can be associated with the same variety of diseases causing dementia; neuroimaging may reveal diagnostic features. At the very early stages of minimal cognitive deficits, differentiation of those patients with early degenerative disease from the worried well or those who are depressed is a significant clinical challenge. Serial imaging with demonstration of progressive cerebral atrophy may be a valuable diagnostic adjunct.

MT-26

Differential diagnosis of dementia

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Dementia is operationally defined as deterioration in more than one cognitive domain below the premorbid level, severe enough to affect normal functioning. The diagnosis of dementia syndrome is made clinically. The first step in the diagnostic process is the establishment of the presence of dementia. A detailed disease history is the core feature; especially relevant are the mode of onset, the disease course and the chronology of the cognitive and behavioural changes, with emphasis on the lead symptoms. Information from caregivers is of paramount importance since many patients with dementia may deny having any problems. A detailed neuropsychological examination is equally important, as it will reveal the profile of the cognitive deficits. The neurological exam is an essential part of the diagnostic work-up to demonstrate accompanying somatic neurological symptoms. Ancillary investigations help in elucidation of the underlying disorder as well as to reveal any co-existent diseases. The disease history, the profile and chronological sequence of cognitive and behavioural symptoms, the presence and nature of somatic neurological findings and the result of ancillary examinations help in the differential diagnosis. Especially important in the diagnostic process is to exclude reversible and treatable dementias. The most frequent cause of dementia is Alzheimer's disease, which accounts for 2/3 of all dementia cases. Alzheimer's disease is a degenerative disorder characterized by pro-

gressive, limbic type amnesia, initially affecting the storage of new information. The other cognitive domains such as attention, language, visuo-spatial and executive functions are also affected as the disease progresses, resulting in global dementia. A variety of behavioural and psychiatric symptoms can accompany the cognitive symptoms. The differential diagnosis includes other degenerative dementias such as fronto-temporal dementia, focal degenerations, depression and a long list of symptomatic dementias.

Headache and central pain

MT-27

Central mechanisms of pain modulation

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The response to a noxious or potentially noxious stimulus not only depends on the stimulus itself but also on the psychological context in which the stimulus is applied. This may result in either reduced or enhanced pain sensation. Extreme examples of this are placebo and emergency analgesia. Thanks to modern neuroimaging studies, we begin to understand how the psychological state of the organism may alter the incoming sensory signals.

Animal research made in the past three decades has revealed a number of brain areas that are involved in the central modulation of pain, such as the periaqueductal grey, the rostroventral medulla, amygdala and hypothalamus. Most of these structures are also targets of ascending pain pathways and/or are involved in learning and memory processes. Animal studies showed that electrical stimulation of these structures may result in powerful stimulation produced analgesia (SPA). The fact that these analgesic effects can be mimicked by the local administration of opioids and the reversibility by naloxone further suggested the involvement of the endogenous opioid system in SPA. This has led to a number of clinical applications for treatment of intractable pain in man such as deep brain and motor cortex stimulation. Besides the opioid system, other neurotransmitter systems (e.g. the dopaminergic system) are also likely to play an important role.

Central modulation may also result in enhanced responses to pain. Recent neuroimaging studies have shed some light on the mechanisms that may be involved in attention and fear enhanced responses to pain.

MT-28

Central pain syndromes

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Central pain is defined as pain caused by a lesion or dysfunction in the central nervous system. All kinds of lesions can induce central pain. The most common conditions with central pain are cerebrovascular lesions (CVL), multiple sclerosis (MS), traumatic spinal cord injuries (SCI) and syringomyelia. Approximate incidences are 8%, 28% and 30%, respectively, in these diseases. The location is the most important feature of the lesion. All lesions that cause central pain affect the somatosensory pathways. They may be located at any level of the neuraxis.

In stroke and SCI the onset of the pain is often delayed, sometimes as much as 2–5 years. The pain is mostly constant, but it may be intermittent or paroxysmal, and its intensity differs much between patients. In stroke the pain is most frequently a hemipain (75%), whereas in MS it dominates in the legs and feet (90%) with about 36% also experiencing pain in the upper extremities. The most common pain qualities are: burning, aching, lancinating, pricking, lacerating, pressing pain.

Central pain is correlated with sensory disturbances, but not with non-sensory neurologic symptoms. For instance, only about 50% of patients with stroke and MS have paresis. The sensory disturbances are dominated by abnormalities in the sensibility to temperature and pain, and hyperaesthesias that are often painful. Touch and cold commonly increase ongoing pain or evoke pain. Decreased sensibility to touch, vibration and joint movements is also common, but does not appear to correlate with the pain. This observation is the basis for the hypothesis that central pain is caused by lesions of the spinothalamic pathways, including their thalamocortical projections.

Central pain usually responds poorly or not at all to analgesics. Some patients with preserved lemniscal functions obtain relief with TENS. Apart from this, the first line treatments are tricyclic antidepressants and antiepileptic drugs. Complete pain relief is rare, but many patients highly value also a modest pain reduction.

MT-29

Central mechanisms in primary headaches

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The most frequent primary headaches, migraine and tension-type headache, are associated with pain distributed in the first division of the trigeminal nerve and upper cervical territories. Migraine pain was thought for some time to originate from abnormal dilatation of large extra- and intracranial vessels. Since there was little evidence for this in clinical research and in experimental animals excitation of V1 nociceptive fibers surrounding small meningeal vessels could produce neurogenic inflammation that was blocked by most acute anti-migraine drugs, the trigemino-vascular system, the visceral nociceptive arm of the trigeminal system, was proposed to be the culprit for migraine headache. Convergence of trigeminovascular afferents with somatic V1 and C2–3 afferents on trigeminal nucleus caudalis is able to explain referral of pain in the ophthalmic nerve and neck areas. At present, however, evidence for activation of perivascular trigeminal afferents and/or meningeal neurogenesis inflammation is lacking, with the sole possible exception of increased levels of CGRP in internal jugular blood during migraine attacks.

Short Communications

Sunday, October 27

Cerebrovascular diseases 1

SC 101

Sleep apnoea disorder is a vascular risk factor

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Sleep apnoea is defined as a cessation of sleep respiration lasting 10 seconds or longer. Hypopnoea is a 30% reduction in thoracoabdominal effort or flow of air and a 4% drop in oxygen saturation. Sleep apnoea disorder (SAD) usually occurs in overweight individuals who snore loudly, have a thick neck and abdominal obesity. The prevalence of SAD in the general population has been estimated at 4% in men and 2% in women. SAD is a risk factor for the development of systemic hypertension, in itself a major risk factor for myocardial infarction and stroke. Several major epidemiological studies have shown a dose-response relationship between the severity of SAD (as measured by the respiratory disorder index and the desaturation index) and the odds ratio for development of systemic hypertension. There is proof that successful correction of the SAD with CPAP applications lowers the mean blood pressure. Patients with moderate to severe SAD are also at risk for development of nocturnal cardiac arrhythmias that include sinus arrest, atrioventricular block, premature atrial or ventricular contractions, and atrial fibrillation. There is evidence that during the apnoea event there is a decrease in mean cerebral blood flow as measured by intracranial ultrasonography; this phenomenon may contribute to stroke. Following stroke, patients have a high prevalence of SAD that further increases the risk of secondary stroke and heightens mortality. In patients with advanced SAD, altered cerebral evoked potentials are not corrected with CPAP applications suggesting permanent cerebral structural damage.

SC 102

The prognostic significance of CT density changes in established cerebral infarcts

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Introduction CT density changes reflect the severity of ischaemic damage after stroke. However, the effect of time influences the visibility of infarcts. This prospective study analyses if the degree of CT hypodensity at 2 time intervals after stroke has a predictive value on the clinical outcome.

Method The study was restricted to 150 patients displaying an anterior circulation syndrome. All patients had CT scans without contrast enhancement on day 3 (± 8 h) and on day 10 (± 8 h) after stroke onset. The degree of hypodensity of the in-

farct was expressed in percentages comparing the Hounsfield's units, determined in the centre of the infarct area to the corresponding zone in the contralateral hemisphere. The modified Rankin scale subdivided the patients, according to their degree of disability at 3 months in R 0–1, R 2–3, R 4–5, R 6.

Result Patients R 4–5 and R 6 had the most severe impairment upon admission. The average density change on CT day 3 was not different between the 4 groups, but the hypodensity was significantly more pronounced on day 10, according to the severity of the disability. CT density increased between days 3 and 10 in R 0–1, was unchanged in R 2–3 and further decreased in R 4–5 and R 6.

Conclusion CT density of the infarct on day 10, but not on day 3, has a prognostic significance. Increase of CT density on day 10 is known as fogging effect and appears as a favourable prognostic factor.

SC 103

Pure lateral medullary infarction: clinical, MRI and angiographic correlation of 130 acute, consecutive patients

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Introduction Although there were a few attempts to make clinical-MRI correlation in patients with lateral medullary infarction (LMI), studies with a large number of patients are unavailable.

Method We analysed clinical features, MRI findings and angiogram results of 130 acute, consecutive patients with pure LMI. MRI identified lesions were classified rostro-caudally as rostral, middle and caudal, and dorso-ventrally as typical, ventral, large, lateral and dorsal. These results were correlated.

Results Patients with rostral MRI lesions more often had dysphagia and facial paresis ($p < 0.01$, respectively), and less often had nausea/vomiting and headache ($p < 0.05$, respectively) than those with caudal lesions. Typical, ventral, large, lateral and dorsal types were correlated with ipsilateral trigeminal, contralateral trigeminal, bilateral trigeminal, isolated limb/body and isolated trigeminal sensory patterns, respectively. Patients with large type lesions more often had dysphagia, hoarseness and dysarthria ($p < 0.01$, respectively) while those with ventral type lesions less often had severe gait ataxia ($p < 0.01$), than those with other type lesions. Angiogram showed vertebral artery disease in 67% and posterior inferior cerebellar artery disease in 10%. The presumed pathogenetic mechanisms included large vessel infarction in 49%, arterial dissection in 15%, small vessel infarction in 13%, cardiac embolism in 5%. Dissection more often occurred in patients with caudal (vs. rostral) lesions ($p < 0.01$) while dorsal type infarcts (vs. other types) were more often related to cardiogenic embolism ($p < 0.05$).

Conclusion We conclude that the three dimensional (rostro-caudal and dorso-ventral) classification helps us understand the clinical and partly, etiopathogenetical aspect of the heterogeneous LMI syndrome.