Cluj-Napoca, 400573 str. Teleorman nr.33 A
tel./fax: +40 264.431924

e-mail: office@ssnn.ro
www.ssnn.ro

9/13/July/2007
ROMANIA

NEUROLOGY SUMMER SCHOOL

SOCIETATEA PENTRU STUDIUL NEUROPROTECȚIEI ȘI NEUROPLASTICITĂȚII

Societatea de Neurologie din România

Neurology Summer School

Romania 9-13 July, 2007

FACULTY/in alphabetical order

Claudio Bassetti	(Switzerland)
Ovidiu Băjenaru	(Romania)
Natan Bornstein	(Israel)
A.V. Ciurea	(Romania)
Laszlo Csiba	(Hungary)
Arnon Karni	(Israel)
Anat Kesler	(Israel)
Amos Korczyn	(Israel)
Torbjörn Lundstedt	(Sweden)
Marie-Helene Marion	(UK)
Dafin Mureşanu	(Romania)
Bogdan Popescu	(Romania)
Hari Shanker Sharma	(Sweden)
Eduardo Tolosa	(Spain)
Pieter E. Vos	(The Netherlands)

PROGRAM

Monday 09.07.07 **Dementia**

08:15-08:30	Introduction - Dafin Mureşanu and Ovidiu Băjenaru
08:30-09:15	Opening Lecture - Hari Shanker Sharma - Blood-brain barrier - the gateway to neurological diseases and neuroprotection
09:15-10:00	Claudio Bassetti - Narcolepsy
10:00-10:30	Coffee break
10:30-11:15	Claudio Bassetti - Sleep and stroke
11:15-12:00	Amos Korczyn - Vascular cognitive impairment
12:00-12:45	Amos Korczyn - Dementia in Parkinson 's disease
12:45-13:30	Bogdan Popescu - Pathogenic mechanisms in dementia: beyond beta-amyloid and tau
13:30	Lunch
18:30-21:30	Dementia - Case presentations and discussions

PROGRAM

Tuesday 10.07.07 **Stroke**

08:30-09:15	Opening Lecture - Torbjörn Lundstedt - Multivariate design strategies for development of neuroprotective compounds
09:15-10:00	Natan Bornstein - Secondary stroke prevention
10:00-10:45	Dafin Mureşanu - A Holistic approach on neuroprotection and neuroplasticity, applied in stroke treatment
10:45-11:15	Coffee Break
11:15-12:00	Laszlo Csiba
12:00-12:45	Natan Bornstein - Management of acute ischemic stroke, the hyperlink (HYPER - tension, termia and glycemia)
13:30	Lunch
18:30-21:30	Stroke - Case presentations and discussions

Wednesday 11.07.07 **Neuroimmunology**

08:30-09:15	Marie-Helene Marion - Botulinum toxin treatment in movement disorders of oropharyngeal muscles, cervical dystonia and limb dystonia
09:15-10:00	Marie-Helene Marion - Botulinum toxin treatment in movement disorders of oropharyngeal muscles, cervical dystonia and limb dystonia
10:00-10:45	Ovidiu Băjenaru - Pathophysiologic mechanism in multiple sclerosis: premise of neuroprotection?
10:45-11:15	Coffee break
11:15-12:00	Ovidiu Băjenaru - Pathophysiologic mechanism in multiple sclerosis: premise of neuroprotection?
12:00-12:45	Arnon Karni - Current and future therapies for MS
12:45-13:30	Arnon Karni - The approach to neutralizing antibodies for interferon beta - unusual cases of demylinating disease of the CNS
13:30	Lunch
18:30-21:30	Anat Kesler - Neuro - Ophtalmology

PROGRAM

Thursday 12.07.07 **Vascular and trauma**

08:30-09:15	Pieter E. Vos - Traumatic brain injury: A challenge for the Neurologist • Early management issues • The post concussion syndrome
09:15-10:00	Pieter E. Vos - Traumatic brain injury: A challenge for the Neurologist • Traumatic Brain Injury - How to read the CT • Diffuse axonal Injury
10:00-10:45	Dafin Mureşanu - Neuroprotection and neuroplasticity in traumatic brain and spinal cord injury
10:45-11:15	Coffee break
11:15-12:00	A.V. Ciurea - Intracranial aneurysm - multimodal treatment, prevention and neuroprotection of perioperatory stroke, global outcome
12:00-12: 45	Natan Bornstein - Management of symptomatic carotid stenosis - CEA vs. Stent
13:30	Lunch
18:30-21:30	Neuroimmunology - Case presentations and discussions

Friday 13.07.07 **Movement disorders**

08:30-10:00	Eduardo Tolosa - Non motor manifestations in PD
10:00-10:30	Coffee break
10:30-11:30	Eduardo Tolosa - Case presentations and discussions
13:00	Lunch
14:30	**Written examination**

NARCOLEPSY

CLAUDIO BASSETTI / Neurology Department, University Hospital Zurich, Zurich, Switzerland

Narcolepsy is a long-life, usually sporadic (rarely familial) sleep-wake disorder characterized by an often disabling excessive daytime sleepiness (EDS) and so-called REM-sleep symptoms such as cataplexy (muscle tone loss triggered by emotions), sleep paralysis and hallucinations.

Biological markers of narcolepsy are a specific HLA class II-subtype (DQB1*0602), the appearance of REM-sleep within 1520' after sleep onset (so called sleep onset REM periods or SOREM) and the absence/reduction of the recently discovered peptide hypocretin-1 (also called orexin-A) in the cerebrospinal fluid.

The neurobiology of narcolepsy has traditionally been attributed to a neurochemical (cholinergic-aminergic) dysbalance in the brainstem, based on genetic predisposition and environmental factors.

The involvement of the hypocretin system in both human and animal forms of narcolepsy has led to the recognition of a central role of the hypothalamus in the pathophysiology of this disorder. Treatment of narcolepsy includes counselling, scheduled naps, stimulant as well as anticataplectic drugs.

This presentation reviews clinical features, diagnostic criteria, pathophysiology and therapeutic strategies of human narcolepsy, also integrating the most recent data on the physiology and pathology of hypocretinergic neurotransmission.

SLEEP AND STROKE

More than 50% of stroke patients have sleep-disordered breathing (SDB), mostly in the form of obstructive sleep apnea (OSA). SDB represents both a risk factor and a consequence of stroke.

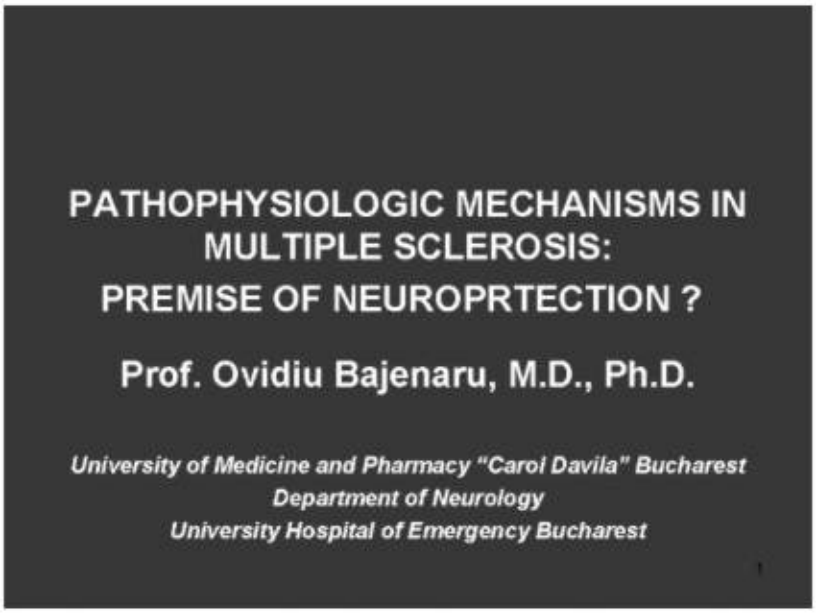
The presence of SDB has been linked with poorer long-term outcome and increased long-term stroke mortality. Continuous positive airway pressure is the treatment of choice for OSA. Oxygen and other forms of ventilation may be helpful in other (e.g., central) forms of SDB.

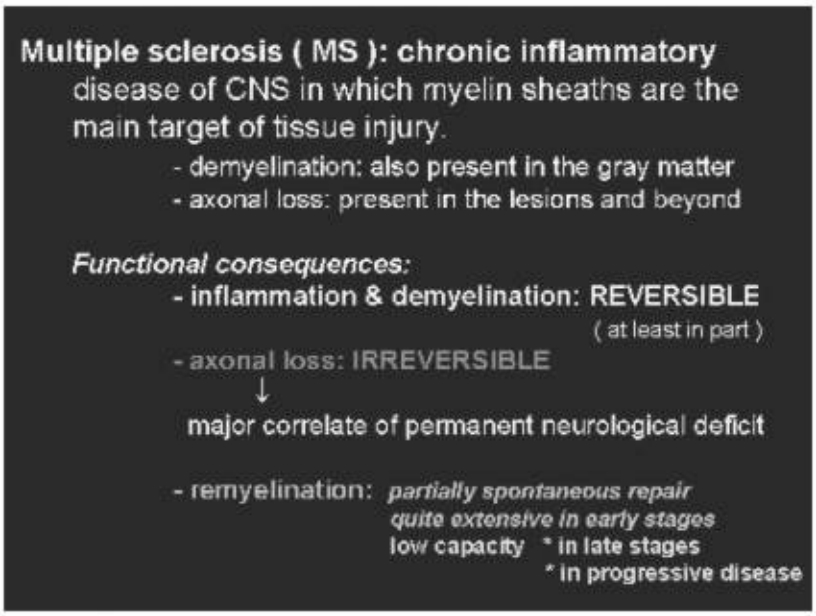
SDB can improve spontaneously after stroke. About 20 to 40% of stroke patients have sleep-wake disorders (SWD), mostly in form of insomnia, excessive daytime sleepiness/fatigue, or hypersomnia (increased sleep needs). Depression, anxiety, SDB, stroke complications, and medications may contribute to SWD and should be addressed first therapeutically.

Brain damage per se, often at thalamic or brainstem level, can be also a cause of persisting SWD. In these patients, hypnotics, dopeminergic agents, and stimulants (e.g., modafinil) can be attempted.

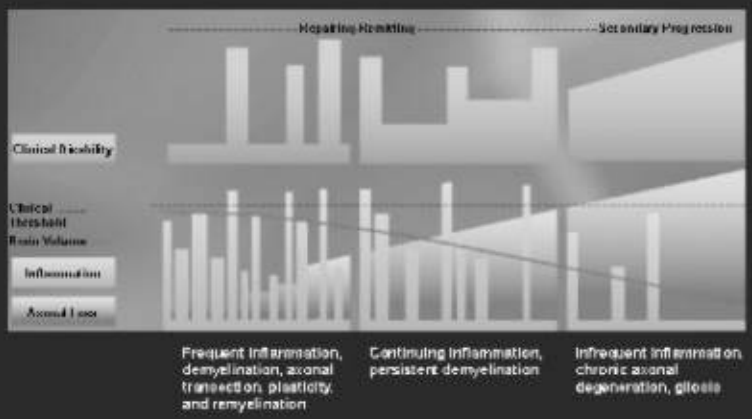
PATHOPHYSIOLOGIC MECHANISM IN MULTIPLE SCLEROSIS: PREMISE OF NEUROPROTECTION?

OVIDIU BĂJENARU / Department of Neurology, University Hospital Bucharest, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania





Inflammation and Axonal Loss in MS



Compston A, Coles A. Lancet. 2002;359:1221-1231

Recent Progress in Understanding Pathogenesis and Therapeutic Implications

- **Disease Heterogeneity: 4 main disease subtypes**
  Need of better diagnostic tools for in vivo distinction
- **Variable genetic background and susceptibility may impact on treatment response**
  Need for molecular diagnostics to guide treatment decisions
- **Changing relation of Inflammation – Neurodegeneration**
  Phase adapted choice of treatment targets
- **Strategies for rehabilitation**

Kappos L., 2006

- GENETIC and ENVIRONMENTAL FACTORS:

  * may facilitate the movement of autoreactive T cells and demyelinating Ab's from the systemic circulation into the CNS through disrupting of BBB

  * in the CNS: local factors may up-regulate expression of endothelial adhesion molecules (ICAM-1, VCAM-1, E-selectin), further facilitating the entry of T-cells into the CNS

- IMMUNOLOGIC/ INLAMMATORY CASCADE:

  * implying: - inflammatory cells from systemic circulation
    - macrophages (→ systemic circulation & microglia)
    - astrocytes
    - cytokines, chemokines, complement, Ig's, proteases

  * affecting - myelin sheath
    - axons
    - oligodendrocytes

Microglia activation

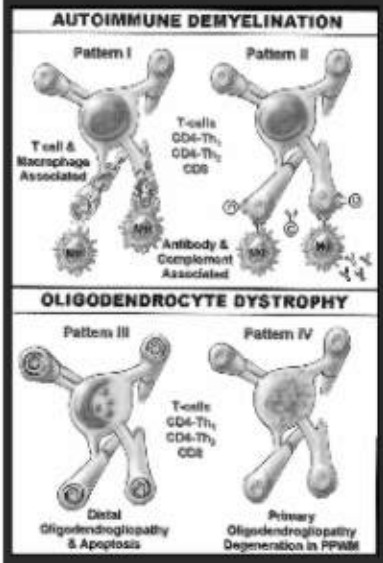
The presence of activated macrophages and microglia is correlated with the extent of neuronal injury in EAE mice

In areas occupied with activated microglia:
* sparse fibers and axonal loss were generally evident

In adjacent areas of nonactivated microglia:
* neuronal structure seems intact

Peripherally originated macrophages are also involved

Aharoni R et al, The Journal of Neuroscience, 2005



Different immunological patterns involved in demyelination & tissue distruction:

I. mainly mediated by T-lymphocytes & activated macrophages and microglia

II. prominent involvement of Abs and complement

III. features hypoxia-like tissue injury

IV. severe involvement of oligodendrocytes: increased susceptibility of these cells for immune-mediated injury

Lucchinetti C.F. et al, 2000, 2005

7

AXONAL LOSS:

Factors associated with axonal damage:

- Cytokines
- NO
- Proteases
- Superoxids
- $CD8^+$ T cells
- Glutamate excitotoxicity
- Microglia *(through cholesterol-breakdown products)*

Werner P et al, Ann Neurol, 2001
Diestel A et al, J Exp Med, 2003

8

AXONAL LOSS (1):

1. IN ESTABLISHED LESIONS:
   - A. active demyelination
     - earliest signs of axonal injury:
       disturbance of fast axonal transport
       ⇓
       * focal accumulation of APP at the site of injury
       * focal axonal swelling
   - B. inactive demyelinated plaques
     - additional slow burninig axonal injury and loss
       (ABSENT WHEN PLAQUES ARE REMYELINATED !)

2. IN NAWM & PROGRESSIVE FORMS:
   diffuse inflammatory process **throughout the whole brain and spinal cord, associated with** diffuse axonal injury & loss, followed by fiber demyelination & secondary myelin distruction **(extensive activated local microglia with increased expression of iNOS and oxidative stress)**

9

AXONAL LOSS (2):

Disruption of axonal continuity
⇓
(outside the plaques)
degeneration of distal portion of the nerve fiber
&
in addition, retrograde degeneration
(+ intracortical demyelinating lesions)
⇓
BRAIN & SPINAL CORD ATROPHY

10

AXONAL LOSS (3):

When axons lose their myelin sheaths:

1. Na^+ channels primary located at the former nodes of Ranvier, redistribute along the whole internode ⇒ CONDUCTION BLOCK
2. Changes in the expression of Na^+ channels subtypes: disturb the functional properties of demyelinated axons
3. Other molecules located at the myelin/ axon interface show abnormalities in demyelinated MS plaques: ABNORMALITIES EXTENSION BEYOND THE BORDERS OF PLAQUES
4. Disturbed axonal transport in acutely injured axons:
   - accumulation of N-type voltage-gated Ca^{++} channels
5. Abnormalities in surviving axons: severe changes in composition and function: cytoskeletal proteins deranged

Lassmann H., 2005 [11]

In the chronic lesions of MS appear:

- differentiation of oligodendrocytes to a premyelination type
- association of premyelinating oligodendrocytes with axons
- expression of myelin oligodendrocyte glycoprotein (MOG)

but:

NO MYELINATION !

Possible causes of inhibition of myelination in MS chronic lesions:

- dysregulated growth factors ?
- altered molecular composition of axons ?
- the presence of an inhibitory signal ?

Studies suggest:

- dystrophic axons limit the remyelination of MS chronic lesions

(abnormal molecular composition / imbalance of GF that regulate myelination)

Chang A. et al, NEJM, 2002 [12]

In the chronic lesions of MS:

- a number of growth-inhibiting substaces: in the gliotic scar of chronic MS plaque → perpetuate development arrest precluding axonal outgrowth & myelin repair
- agonists produced by oligodendrocytes (Nogo, MOG) for Nogo-receptors → arrest of axonal growth
- Nogo-receptor blockade might promote axonal regeneration *(possible future therapeutic strategy of MS)*

Frohman E.M. et al. NEJM, 2006

13

Mechanisms of axonal injury and targets for neuroprotection

Kappos L., 2006

- Excitotoxic mechanisms:
  1. Glutamate overactivation
  2. Ca^{++} influx
  3. Na^{+} influx
- Inflammatory mechanisms:
  1. Nitric oxide
  2. CD8+ cytotoxicity
  3. TNFα, PGE_2
  4. Proinflammatory cytokines
  5. Antibodies
  6. Oedema
- Demyelination induced:
  1. Increased vulnerability to damage of demyelinated axons
  2. Dying back mechanism
- Energy depletion:
  1. Mitochondrial dysfunction
  2. Free radicals
- Genetic determination:
  1. Genetic programme
  2. Degeneration
- Apoptotic mechanisms:
  1. Caspase pathway
  2. Other
- Depletion of growth factors:
  1. Depletion of stem cells
  2. Lack of inflammatory cells which may produce GF

14

Neuroprotection strategies in MS

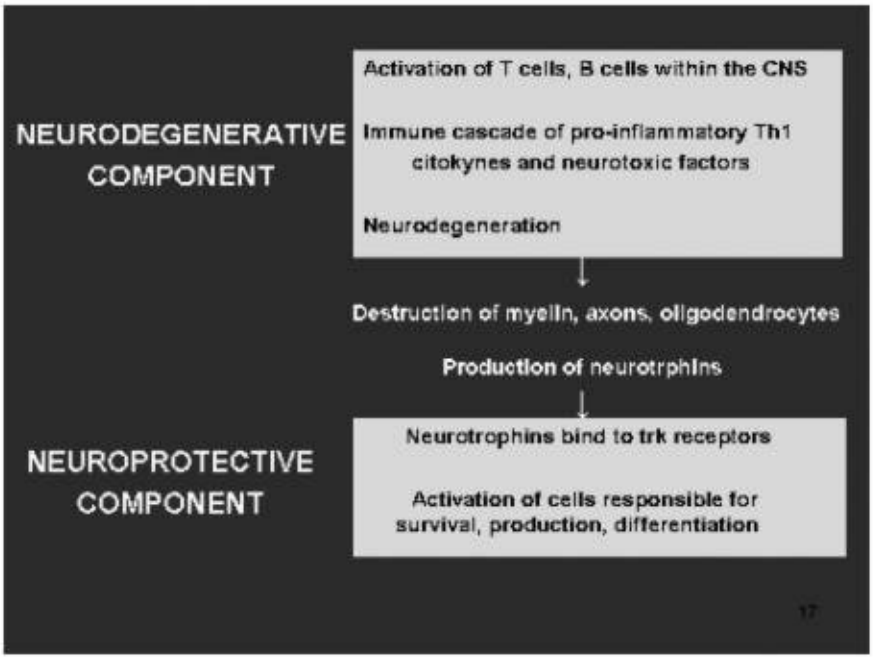
- anti-inflammatory treatment
- anti-demyelinating treatment & promotion of early remyelination
- trophic support for axons

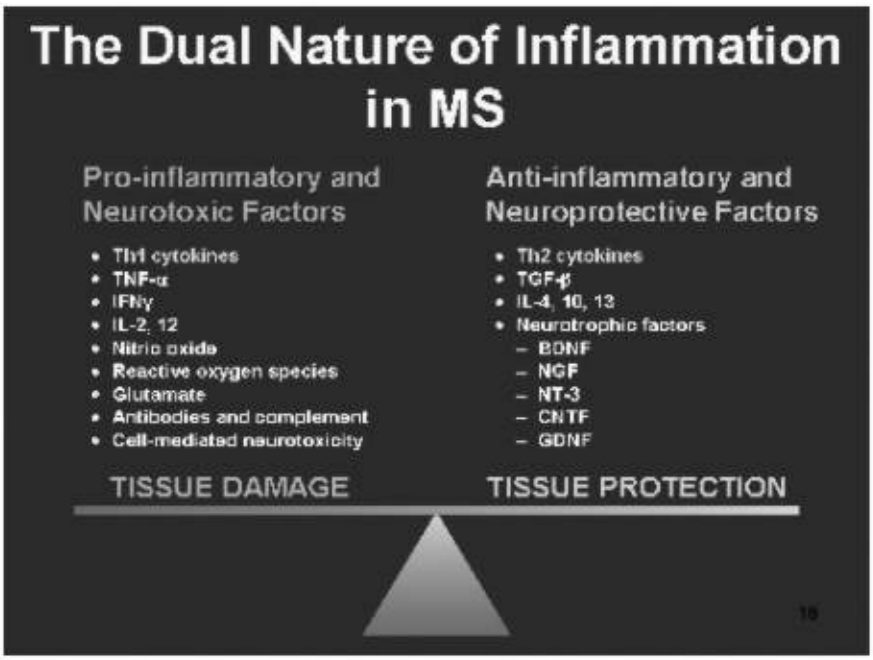
10

Inflammatory Cells May Counterregulate Detrimental Inflammation

- Inflammatory cells produce growth factors
- Inflammatory cells remove myelin-associated inhibitory molecules
- Inflammatory cells may adapt a protective suppressor phenotype

Martino G et al. Lancet Neurology. 2002;1:499-509.


NEURODEGENERATIVE COMPONENT
Activation of T cells, B cells within the CNS
Immune cascade of pro-inflammatory Th1 citokynes and neurotoxic factors
Neurodegeneration
Destruction of myelin, axons, oligodendrocytes
Production of neurotrphins
NEUROPROTECTIVE COMPONENT
Neurotrophins bind to trk receptors
Activation of cells responsible for survival, production, differentiation
17


The Dual Nature of Inflammation in MS
Pro-inflammatory and Neurotoxic Factors
Th1 cytokines
TNF-α
IFNγ
IL-2, 12
Nitric oxide
Reactive oxygen species
Glutamate
Antibodies and complement
Cell-mediated neurotoxicity
Anti-inflammatory and Neuroprotective Factors
Th2 cytokines
TGF-β
IL-4, 10, 13
Neurotrophic factors
– BDNF
– NGF
– NT-3
– CNTF
– GDNF
TISSUE DAMAGE
TISSUE PROTECTION
18

Possible Functions of Neurotrophic Factors - BDNF

- Activated human T-cells, B-cells and monocytes secrete BDNF, which supports neuronal survival in vitro
- In MS lesions, BDNF is present in immune cells and astrocytes
- The BDNF receptor is expressed in neurons in MS lesions and in nearby astrocytes

Kerschensteiner M et al. J Exp Med 1999; 189(5): 865-870.
Stadelmann C et al. Brain 2002; 125: 75-85.

19

PROTECTION OF AXONS VIA FACILITATION OF REMYELINATION (1)

1. Autoreactive Ab's may enhance the endogenous myelin repair
2. The enhancement of remyelination was associated with proliferation or preservation of mature oligodendrocytes

   Prajoutwat & Rodriguez, 1993
3. IgM's that bind to Ag's on the surface of oligodendrocytes exert a direct stimulation of the myelin-producing cells
4. Candidate human monoclonal Ab that might promote remyelination (IgM) have been identified ⇒ generation of a HUMAN RECOMBINANT MONOCLONAL IgM (potential therapeutic agent in patients with MS)

   Warrington et al., 2000

20

CONCLUSIONS (1):

1. DEMYELINATION is necessary but not sufficient for development of permanent deficits in primary demyelinatig disorders of human and animals;

2. DEMYELINATION predisposes axons to subsequent SECONDARY INJURY or LOSS

3. AXONAL INJURY & LOSS: determine secondary myelin distruction

4. INJURY TO THE AXON may result as either:
   - T cell toxicity
   - Failure of neurotrophic support from death by myelinatig oligodendrocytes

21

CONCLUSIONS (2):

5. TERAPEUTIC CONSEQUENCES for neuroprotection:

   * immunomodulatory treatments (IFNβ, GA)

   * promoting neurotrophic factors: GA, IgM

   * transplantation of oligodendrocytes progenitors

   * other patogenic strategies

22

Success in remyelination therapy may be achieved either by:
- enhancing endogenous repair or,
- by grafting exogenous remyelinating cells.

Several neurotrophic factors have been shown to enhance endogenous remyelination

Many immature cells have been shown to induce efficient exogenous remyelination in animal models

Statins, cyclins and immunophilin ligands are orally available immunomodulatory agents that may protect neurones

Other promising possibilities:
- modulation of excitotoxicity
- modulation of nitric oxide synthesis
- modulation of cationic channels

Lubetzki C et al, Curr Opin Neurol. 2005

Despite the increasing number of putative therapeutic targets

- no treatment to achieve remyelination or neuroprotection has yielded positive clinical results in humans

- forging a link between basic biology and treatment of patients will require us to overcome several challenges

  * assessment of efficacy of repair

  * improving tolerance to neurotrophic factors

  * delivery of neurotrophic factors

  * better defining the indications for *and* limitations of transplantation.

Lubetzki C et al, Curr Opin Neurol. 2005

MANAGEMENT OF SYMPTOMATIC CAROTID STENOSIS CEA VS. STENT

NATAN
Israel

Symptomatic severe carotid stenosis (>70%) carries a high risk of subsequent stroke of about ~ 30% over 2 years.
Carotid endarterectomy (CEA) was proved to reduce the risk of stroke significantly, with Relative Risk Reduction (RRR) = 65% and Number Needed to Treat (NNT) = 6 if performed safely (perioperative S&D =5.8%) and should be executed within 2 weeks of TIA or minor stroke (NASCET & ECST).

For carotid stenting to replace CEA we need to know the comparative safety, durability and efficacy of the procedure. Only a few randomized, controlled studies comparing CEA and stenting were conducted (CAVATAS, SAPPHIRE, EVA-3 and SPACE) with inconclusive results. There are still several ongoing studies (CREST in the USA and ICSS in Europe and Australia). Until more data will be available carotid stenting should be performed only in a selected group of patients with specific indications like: re-stenosis of the CEA, post neck radiation, inaccessible lesion for CEA and contra-indications for CEA.

HYPERTENSION IN ACUTE ISCHEMIC STROKE

Despite the prevalence of arterial hypertension following acute ischemic stroke its optimal management has not been established1. Epidemiology observational data show that approximately 77% - 84% of stroke patients have spontaneous elevation of BP in the first 24-48 hours after stroke onset. However, BP elevation typically declines and resolves within few hours or days after onset of stroke.
Several studies have shown the association between elevated admission BP and poor prognosis (morbidity and mortality) of stroke patients and also the association between gradual drop in BP within 48 hours of onset of stroke and good outcome.
Analysis of 17,398 patients of the International Stroke Trial (IST) showed a U shaped curve correlation between BP, death and dependency at 3 months, with 4.2% relative increase in recurrence per 10 mmHg of systolic blood pressure. On the other hand, BP change or large drop in BP during the acute phase of ischemic stroke may result in poor outcome at 3 moths. This effect was observed in the NINDS IV rtPA trial and in the INWEST trial where high dose of nimodipine caused a large drop in BP and therefore worse outcome.
Blood pressure elevation as a treatment for acute ischemic stroke There have been several case reports in the early 50s and 70s about BP augmentation as a treatment for acute ischemic stroke.
This treatment concept is currently being tested in larger clinical trials.
The concept of lowering BP in the acute phase of ischemic stroke was tested in randomized, placebo-controlled study of candasartan, the ACCESS study. There was no difference in stroke outcome at 3 months but the treated group had lower recurrent vascular event rate after one week. There are several ongoing clinical trials testing various BP lowering agents in acute ischemic stroke that are awaiting final results.

In summary, high BP is common immediately after acute ischemic stroke and has detrimental effect on outcome. It is still unclear whether BP should be manipulated and how. Further experimental and clinical trial data are needed in order to clarify how to manage BP in the acute phase of ischemic stroke.

BLOOD GLUCOSE IN ACUTE STROKE: TO ACT OR NOT TO ACT?

Diabetes mellitus is one well-recognized risk factor for stroke. The role and the management of hyperglycemia in the acute phase of ischemic stroke, however, have not been investigated in depth.

EXPERIMENTAL DATA AND MECHANISMS

The data in recent studies on animal stroke models suggest that brain infarction and acute elevation in glucose stores result in aggravation of anaerobic glycolysis and brain tissue acidosis. Studies on hyperglycemic subjects showed aggravated ischemic brain lesions due to raised blood glucose concentrations and its consequences, such as intra- and extracellular acidosis and postischemic alkalosis.

The relative deficit of insulin is another important feature of stroke in hyperglycemic conditions. Finally, it is important to consider the increased amount of circulating free fatty acids that may impair endothelium-dependent vasodilation, a condition associated with heightened risk of stroke.

CLINICAL DATA

Hyperglycemia is a frequent finding in acute stroke patients regardless of their previous blood glucose levels. Williams et al. found that hyperglycemia at admission to hospital was present in 40% of patients with acute stroke and concluded that admitting hyperglycemia was associated with increased short- and long-term mortality as well as with increased inpatient charges.

A more severe hyperglycemic response is more prevalent in patients with hemorrhagic stroke and brainstem infarction compared with patients with cerebral infarction. There are more comatose subjects among hyperglycemic patients and hospital mortality is significantly higher among them . The possible mechanisms of a hyperglycemic reaction following acute stroke could be underlying latent diabetes, hypothalamic dysfunction, increased secretion of growth hormone, irritation of the glucose regulatory centers and non-specific reaction to acute stress and tissue injury with the associated autonomic, hormonal and metabolic alterations.

In a study on 138 stroke patients treated with intravenous rt-PA, admission hyperglycemia was associated with a higher risk of hemorrhagic transformation. A study on 63 acute stroke patients who were prospectively evaluated with serial diffusion-perfusion weighted MRI and acute blood glucose measurements. The hyperglycemia in patients with perfusion-diffusion mismatch was associated with greater acute-subacute lactate production, which, in turn, was independently associated with reduced salvage of mismatch tissue. The authors concluded that acute hyperglycemia increases brain lactate production and facilitates conversion of

hypoperfused at-risk tissue into the infarction, an event that may adversely affect stroke outcome.
The safety of controlling insulin blood glucose levels was initially proved in a small pilot study on 53 acute stroke patients, though any significant difference in outcomes of two groups was noted. In the last published update of this study (The United Kingdom Glucose Insulin in Stroke Trial (GIST-UK) revealed that the GKI infusions reduced plasma glucose and BP. However, these were not associated with significant clinical benefit (Lancet Neurol. 2007 May; 6(5):397-406.
The European Stroke Initiative (EUSI) in new recommendations 2003/2004 suggests immediate insulin titration if an acute stroke patient's blood glucose level reach 200 mg/dl or 10 mmol/l and higher. Unless the blood glucose level is known, no carbohydrate concentration should be given to a stroke patient.

CONCLUSION

There is no doubt that hyperglycemia has a deleterious impact in ischemic stroke. Randomized controlled trials of aggressive glycemic control in acute stroke are needed to better understand the underlying mechanisms of hyperglycemia among these patients. We expect that insulin treatment of suitable stroke patients is likely to become standard practice in their management.

SECONDARY STROKE PREVENTION IN NON CARDIOEMBOLIC STROKE

Patients with TIA or ischemic stroke carry a risk of recurrent stroke between 5 and 20% per year. In patients with TIA or ischemic stroke of noncardiac origin antiplatelet drugs are able to decrease the risk of stroke by 11-15% and the risk of stroke, MI and vascular death by 15-22%. Aspirin is the most widely used drug. It is affordable and effective. Low doses of 50-325 mg aspirin are as effective as high doses and cause less gastrointestinal side effects. Severe bleeding complications are dose-dependent. The combination of aspirin with slow release dipyridamole is superior to aspirin alone for stroke prevention (ESPS-2 and ESPRIT). Clopidgrel is superior to aspirin in patients at high risk of recurrence (CAPRIE). The combination of aspirin plus clopidogrel is not more effective than clopidogrel alone but carries a higher bleeding risk (MATCH and CHARISMA). None of the antiplatelet agents is able to significantly reduce mortality.

SECONDARY PREVENTION OF CARDIOEMBOLIC STROKE

Atrial fibrillation (AF) is the most common cause of cardioembolism. The main line of actions of stroke prevention in AF are antithrombotics, mainly anticoagulant (cumadin) or antiplatelet, antiarrhythmics (for rate control and sinus rhythm restore), mechanical means (for occlusion of the left atrial appendage or protection of the internal carotid artery from emboli). Classic pharmacological prevention with warfarin may be overcome by direct thrombin inhibitors like ximelagatran and others. Recent achievements on endovascular procedures deploying carotid artery implants provide an opportunity to divert emboli to nonhazardous locations, whereas cardiac devices can seal left atrial appendages and avoid risk of clot migration in the blood stream. In the next decade, the challenge will be to understand competitiveness between old and new drugs with endovascular implants.

REFERENCES

Diener H.C, Primary and secondary stroke prevention with antiplatelet drugs. Curr Pharm Des. 2006;12(10):1293-7

Corea F et.al, Secondary prevention of cardioembolic stroke: oldest and newest promises. Clin Exp Hypertens. 2006 Apr-May;28(3-4):413-20.

INTRACRANIAL ANEURYSM MULTIMODAL TREATMENT; PREVENTION AND NEUROPROTECTION OF PERIOPERATORY STROKE; GLOBAL OUTCOME

A.V. CIUREA / Clinical Hospital "Bagdasar-Arseni", Neurosurgical Department, Bucharest, Romania

BACKGROUND

The intracranial aneurysm (I.A.) represent a prevalence between 0,2-7,9% in the literature. The variability depends of hospital referral. Neuroimaging findings and autopsy pattern. The pathology of intracranial aneurysm is a dominant element in neurosurgical activity, because of multiple preoperatory and management problems.
IA affected prepoderently the active age (40 and 60 years old) and the male sex. Generally the incidence in USA is 10-28/100.000 (official data).
The etiology of IA may be: congenital aneurysm (defect of muscular layer of arterial wall), arterial hypertension, neoplastic disease, atherosclerosis, inherited diseases, trauma, infection (mycotic an.), and unknown causes.
In all the cases of aneurysm rupture are incriminated as risk factors: cigarette smoking, alcohol excess, life stress.
The cerebral circulation must be evaluated in totality and aneurysms in particular and the accuracy management is necessary for limitation of important lifethreatring complication (rebleeding and ischemic stroke).

MATERIAL & METHODS

The author present a study about 468 consecutive operated patients with intracranial aneurysms, operated in first Neurosurgical Department between 1997-2006 10 years - (30 children and 438 adults). Most cases (213 cases-45,5%) were between 41 and 50 years old. The predominant sex is male 318 cases (68%) (2,1 : 1). The symptoms were dominated by: headache (98%), stiffneck (94%) and focal neurologic deficit (91%). Most patients were Hunt and Hess 2 (172 cases, 36,7%), Hunt and Hess 3 (72 cases, 15,4%) at admittance. The associated pathology was: systemic arterial hipertension (351 cases, 75%) and obesity/hypercolesterolemia (160 cases, 34,1%), ischemic cardiopathy (75 cases,16%), diabetus melitus (75 cases,16%), chronic alcoholism (61 cases,13%), ischemic stroke (56 cases,12%), atrial fibrilation (47 cases, 10%), miscellanea (66 cases, 14%, anticoagulant therapy).
The main investigations were: CT scan, DS angiography. Actually, the most important were 3D DS Angiography and 3D CT Angiography.
The common localization of intracranial aneurysms was the anterior communicating artery 165 cases (35,3 %); the other locations were: medium cerebral artery 139 cases (29,7%), posterior comunicating artery 74 cases (17,9%), internal carotid artery 62

cases, (13,3%), basilar top 8 cases (1,8%) and vertebral artery 8 cases (1,8%). All cases was operated, as soon as possible after the subarachnoid hemorrhage (SAH) and IA angiography diagnosis. "Early surgery" eliminates the risk of re-bleeding and facilities the treatment of vasospasm which peak is between 6-8 days post SAH.
From all complications two are very critical for life and morbidity: aneurysm rebleeding and cerebral ischemia.
The therapeutical operative measures for intraoperatory aneurysm rupture prevention are: mild hyperventilation (PaC02 30-35 mmHg); elevation of the head; deliberate hypotension; temporary clip. The most important intraoperatory aneurysms surgery is the perfect microsurgical approach which realized the perfect aneurysm dissection with all perforates, collaterals and magistral arteries; the clip application on the aneurysm neck is the surgical procedure to cure the vascular malformation (gold standard - aneurysm obliteration). Other methods represent wrapping or coating the aneurysm, but all this is generally inefficient. Also as intraoperative neuroprotective measures we mention: local papaverine solution administration, abundant saline water washing.
During postoperative period we noticed the following complications: vasospasm, obstructive hydrocephalus, seizures, cerebral edema, and general complications.
The following neuroprotective measures for postoperative complications preventions are: 3H therapy (hypertensive therapy, hypervolemic, hemodilution). Nimotop therapy could be used in preoperative period also, for cerebral ischemia prevention. (3-7 ml/h depends on arterial systemic pressure), but 3H therapy could be applied with maximum efficiency only in postoperative period (after aneurysm clipping).
The Glasgow Outcome Scale (GOS) in our data (at 6 months postoperator) shows: good recovery 313 cases (66.8%), moderate disability 110 cases (23.6%), severe disability 23 cases (4.9%), persistent vegetative state 5 cases (1.1%), death 16 cases (3.5%).
Actually, an important number of IA will be treated by endovascular embolization. The Guglielmi detachable coils (GDC) represent an elctrolytically detachable platinum coils placed via endovascular techniques. This GDC is feet for vertebro-basilar aneurysm in which the open microsurgical approach is difficult. Our experience in first neurosurgical clinic consist in 24 cases of embolization. Also in this procedure appears many complication: aneurysm rupture, cerebral ischemia, neurological deficit and consciousness status modification.

CONCLUSIONS:

IA represents an important neurosurgical challenge. Also IA by the rupture and complication is the real lifethreatering diseases. Clincal features are dominated by

SAH & neurological signs (Hunt and Hess scale-1968, was perfectly useful).
Complete vascular exclusion is the treatment of choice by open microsurgical approach or endovascular embolization.
The important measures to avoid rebleeding and cerebral ischemic stroke in intracranial aneurysms are perfect evaluation and early approach, perfect aneurysm dissection and neuroprotective measures (pre, intra and postoperatory). Neuroprotective agents useful to avoid cerebral ischemic stroke The timing of aneurysm surgery is one of the key of avoidance lifethreatring complication

KEYWORDS:
Intracranian aneurysms, subarachnoid hemorrhage, Hunt & Hess Scale, 3D CT Angiography microsurgery, embolization, rebleeding, vasospasm, Nimotop, neuroprotection, 3H therapy.

LASZLO CSIBA / Debrecen University, Department of Neurology, Debrecen, Hungary

THERAPY FOR MULTIPLE SCLEROSIS: PRESENT AND FUTURE

ARNON KARNI / Dept. of Neurology, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel

Multiple sclerosis (MS), a chronic inflammatory disorder of the central nervous system (CNS), results in damage to axons and their surrounding myelin sheath. The exact cause of inflammation remains unclear, but an autoimmune response directed against CNS antigens is suspected. Although the exact pathogenesis of MS is not fully understood, current knowledge has already led to the development of effective treatments, namely interferon-1 (IFN-1) and glatiramer acetate (GA), both of which have been shown to reduce relapse rates and disability progression as well as to be safe, and tolerable medications. Some of the IFN-1 treated patients produce neutralizing antibodies against IFN-1 (NABs) which may block the beneficial effect of IFN-1 treatment. A comprehensive approach to the NABs detection and patients manegment should be established. Recent study found that therapy with monoclonal antibodies against the adhesion molecule VLA-4 on monomuclear cells, namely natalizumab (tysabri) dramatically reduce relapse rates and disability progression. However, the fear of progressive multifocal leukoencephalopathy as a possible serious side effect of this medication led to a cautious approach in prescribing this medication. Many clinical trails with new therapies for MS is now conducted, some of them had showed a promising preliminary results

NEURO - OPHTHALMOLOGY

ANAT KESLER / Tel Aviv Sourasky Medical Center, Tel Aviv, Israel

Neuro-ophthalmologists take care of visual problems that are related to the nervous system; that is, visual problems that do not come from the eyes themselves we will discuss two topics:

1. Papilledema ,Pseudopapilledema , the differential diagnosis of these conditions. Idiopathic intracranial hypertension (Pseudotumor cerebri) is a disorder increased intracranial hypertension of unknown etiology. It affects predominantly obese women of childbearing age. We will present cases discuss the clinical picture diagnosis and management.

2. Optic neuritis is the most common acute optic neuropathy in people age 18-45, may be the first indication of multiple sclerosis

We will present case and discuss the clinical picture and the treatment.

DEMENTIA IN PARKINSON'S DISEASE

AMOS D. KORCZYN / Sieratzki Chair of Neurology Sackler Faculty of Medicine, Tel-Aviv University Medical School Ramat-Aviv, Israel

Advanced Parkinson's disease (PD) is frequently associated with dementia. The pathogenesis of this dementia is complex, related to deficiency of several biogenic amines and cortical Lewy body deposition, as well as co-existent age related brain changes, both of the Alzheimer's type and vascular. However, degeneration of the cholinergic neurons in the nucleus basalis of Meynert may have an important contribution to the cognitive decline.

The dementia of PD has a grave effect on the quality of life of the patients and their caregivers, as well as negative effect on their survival.

The treatment of dementia associated with PD therefore must encompass several agents. Cholinesterase inhibitors, such as rivastigmine, produced gratifying results. Future studies should define the exact role of this agent in the treatment of the dementia of PD.

VASCULAR COGNITIVE IMPAIRMENT

Epidemiological data have demonstrated that risk factors for vascular disease in general, and for stroke in particular, are largely identical to those of Alzheimer's disease (AD). Thus, hypertension, diabetes mellitus and elevated serum levels of cholesterol and homocysteine contribute to the occurrence of both diseases. The brain of elderly people accumulates amyloid, neurofibrillary tangles, as well as vascular lesions, large and small, cortical and deep. Blood vessels may manifest lipohyalinosis and result in leucoaraiosis. Cognitive decline in old age results from this cumulative burden. The clinical distinction between vascular dementia and AD is clinically impossible in most cases, is confusing and counterproductive. Most elderly patients with dementia do not have a monolithic pathologic disorder (e.g. AD or vascular dementia) but rather a combination of both. This overlap is supported by imaging evidence as well as by neurochemical markers. Unfortunately, mixed dementia, the most common cause of dementia, is not yet defined clinically or pathologically. Public health measures should be taken to lower the impact of the risk factors responsible for these diseases (such as hypertension, hyperlipidemia, hyperhomocysteinemia, and smoking). Attention to these risk factors by drugs and lifestyle is important in reducing the incidence and prevalence of dementia.

MULTIVARIATE DESIGN STRATEGIES FOR DEVELOPMENT OF NEUROPROTECTIVE COMPOUNDS

TORBJÖRN LUNDSTEDT,[A] PER LEK[B] ,ELISABETH SEIFERT[B], ARNE BOMAN[B] AND HARI SHANKER SHARMA [C] /

a: Acure Pharma AB, Ulleråkersvägen 38, SE 756 43 Uppsala, Sweden; Department of Pharmaceutical Chemistry, Uppsala University, Box 574, BMC, SE 751 23 Uppsala, Sweden; Research Group for Chemometrics, Organic Chemistry, Umeå University, SE-901 87 Umeå, Sweden
b: Acure Pharma AB, Ulleråkersvägen 38, SE 756 43 Uppsala, Sweden
c: Laboratory of Cerebrovascular Research, Department of Surgical Sciences, Anaesthesiology and Intensive Care Medicine, University Hospital, Uppsala University, SE-75185 Uppsala, Sweden

In drug development research combinatorial chemistry has become an integrated part in the drug development process. Roughly 20 years of combinatorial chemistry has resulted in a change of making fewer compounds instead of aiming for synthesis of all possible combinations. Hence, practical limitations usually make it necessary to select smaller subsets of compounds (10-100) to synthesise and test. The proposed strategy for constructing diverse chemical libraries with optimal information, while still taking experimental and practical feasibility into account, is to use statistical experimental design. The objective is to provide optimal chemical diversity while limiting the number of compounds as much possible. With fewer compounds the compounds can be tested as single entities as well as enabling a more elaborate response testing early on in the development towards a desired goal, e.g. an active drug or a good tablet formulation. This strategy is based on a multivariate characterisation of the starting materials (building blocks, reactants, ingredients, excipients, medium *etc.*), Principal Component Analysis (PCA), multivariate design, and Multivariate Quantitative Structure-Activity Relationships (M-QSAR). The presented strategy is general and applies to investigations of design of chemical libraries in solution as well as on solid phase.
A general outline of the strategy will be given from our development of neuroprotective compounds.

BOTULINUM TOXIN TREATMENT IN MOVEMENT DISORDERS OF OROPHARYNGEAL MUSCLES, CERVICAL DYSTONIA AND LIMB DYSTONIA

MARIE-HELENE MARION / Consultant neurologist and honorary senior lecturer, ST George's Hospital, London, UK

A HOLISTIC APPROACH ON NEUROPROTECTION AND NEUROPLASTICITY, APPLIED IN STROKE TREATMENT

DAFIN F. MUREŞANU / Department of Clinical Neurology, University of Medicine and Pharmacy, Cluj-Napoca, Romania

Neuroprotection and neuroplasticity, processes that are apparently independent, with different control, represent in fact two sequences of the same process.
Every lesion triggers a neuroprotective endogenous reaction, after a latency period. A reparatory endogenous process (known as endogenous neuroplasticity) follows this answer also.
Continuously understanding the nature of both forenamed processes, and the manner of switching from neuroprotection to neuroplasticity, will lead to the improvement of specific pharmaceutical strategies.
This presentation analyzes, on one hand, the fundamental biological processes that are continuously going on in the nervous system (neuroprotection, neuroplasticity, neurotrophicity and neurogenesis), and, on the other hand, the molecular pathophysiological mechanisms (excitotoxicity, inflammation, misfolding proteins, apoptosis like processes, free radicals, etc.). Another goal of this presentation is to present and analyze the perspectives of basic and clinical researches in this field.
Although there is an increasing number of available treatments, only a very few molecules had some positive outcomes.
The causes of the unsatisfactory results of the clinical studies are divided in two major categories: the first category is directly related with the complexity of the pathophysiological cascades that cannot be controlled with a single molecule that targets a single mechanism (wrong strategy). The second category is related with the transfer modality from the experimental research in clinical research and with the incorrect design of the clinical studies.
Neurotrophic factors are among the few active molecules that positively control both processes.
Because neurotrophic factors manage to control the sensitive balance of the two named processes, their chances of large-scale applicability as a treatment in different neurological disorders are highly significantly.

NEUROPROTECTION AND NEUROPLASTICITY IN TRAUMATIC BRAIN AND SPINAL CORD INJURY

Neurotrophicity, neuroprotection, neuroplasticity are strategic concepts involved in the maintenance of nervous system functions. They work together to counteract excitotoxicity, free radicals, metabolic dysfunction, inflammation apoptosis-like processes, protein misfolding or genetic conditions.

The strategy of neuroprotector treatment is to interfere with molecular cascades which determined neuronal dysfunction and death. There are two main cell death patterns: necrosis and apoptosis. Only the apoptosis processes, spanning over a longer period of time can be targeted by neuroprotective strategies.

Three major processes should be considered extremely important in the pathophysiology of TBI: excitotoxicity, inflammation, apoptosis like processes. There are compelling evidences indicating that both inflammatory cells and mediators may also have beneficial functions assisting in repair and recovery processes. The neuroprotective capabilities of the inflammation are both absolute and relative. Over the past decades our understanding of the pathophysiology of traumatic brain injury (TBI) has greatly increased and based on this understanding numerous pharmacological therapies have been developed, tested and proven effective in the treatment of experimental TBI.

High concentrations of extracellular glutamate have been demonstrated in both experimental models and clinical patients with TBI. Experimental research identified a number of glutamate antagonists acting either pre- or postsynaptically ionotropic (NMDA, AMPA, etc) or metabotropic receptors, in a competitive, noncompetitive or modulating way.

Mitochondrial dysfunction can be attenuated by inhibitors of mitochondrial permeability transition.

Erythropoietin, hormones, bradykinin antagonists, inhibitors of nitric oxide synthases are the most important molecules proved to exert a neuroprotective activity.

Most clinical trials of neuroprotective agents in stroke, trauma and neurodegenerative disorders are likely to fail in large part because of problems that begin during preclinical development and continue through to the clinical trial design phase and beyond, and here is where the attention should be focused in the nearest future.

PATHOGENIC MECHANISMS IN DEMENTIA: BEYOND BETA-AMYLOID AND TAU

BOGDAN O. POPESCU / Department of Neurology, University Hospital, Bucharest, Romania"Victor Babeş" National Institute of Pathology, Bucharest, Romania

More than one hundred years ago Alois Alzheimer described the pathologic hallmarks of the disease which nowadays bears his name: the senile plaques and the neurofibrillary tangles. Still our effort to understand Alzheimer's disease (AD) is based on the excessive generation of beta-amyloid, which is found within the plaques, and on the abnormal hyperphosphorylation of the microtubule associated tau protein, which form the tangles. However, these two neuropathological findings are not unique to AD, being found with a different distribution and frequency in other forms of dementia as well. Moreover, numerous studies in the recent years showed that other pathogenic mechanisms, like inflammation and microglia activation, alteration of the microvasculature and of the brain-blood barrier, disturbance of the cell cycle, oligodendrocyte damage and synapse alteration, cholesterol transport changes could be important determinants of AD. Therefore, the relationship between the classical and apparently secondary pathogenic factors will be discussed in this paper.

BLOOD-BRAIN BARRIER. THE GATEWAY TO NEUROLOGICAL DISEASES AND NEUROPROTECTION

HARI SHANKER SHARMA / Laboratory of Cerebrovascular Research, Department of Surgical Sciences, Anesthesiology & Intensive Care Medicine, University Hospital, Uppsala University, Uppsala, Sweden

The microenvironment of the central nervous system (CNS) is precisely and meticulously maintained by a set of dynamic physiological barriers located within the cerebral microvessels of the brain (Blood-Brain Barrier) and spinal cord (Blood-Spinal Cord Barrier) as well within the epithelial cells of the choroid plexus separating the blood and cerebrospinal fluid (CSF) interface (Blood-CSF-Barrier). The physicochemical properties of these cellular barriers are quite comparable to that of an extended plasma membrane. The BBB and the BSCB are quite tight to small molecules (12 Å, Lanthanum ion), whereas BCSFB is less restrictive in nature. On the other hand, the ependymal cell linings of the cerebral ventricles and spinal canal, referred to as CSF-Brain Barrier do not normally restrict passage of several small sized molecules. However, protein transport across these barriers is severely restricted. Entry of proteins into the CNS microenvironment induces vasogenic edema formation that is primarily responsible for cell and tissue injury. These blood-CNS-Barriers (BCNSB) are often compromised under a wide variety of psychological, traumatic, metabolic, ischemic, environmental or chemical insults leading to neuronal, glial and axonal damage. Opening of the BCSNB to various endogenous or exogenous substances and proteins alters the molecular, cellular, biochemical, immunological and metabolic environment of the CNS leading to abnormal neuronal function and brain pathology. This review is focused on current status of the BCSNB breakdown in experimental models of emotional stress, traumatic injuries, psychostimulants as well as key environmental health hazards, i.e., heat and/or nanoparticles exposure. Breakdown of the BCNSB in these conditions altered gene expression and induced brain pathology and neurodegeneration. Attenuation of the BCNSB disruption with drugs, antibodies or growth factors markedly reduced the development of brain pathology. Taken together, these observations strongly indicate that the BCNSB can be considered as a "gateway" to the neurological diseases.

NON MOTOR SYMPTOMS OF PARKINSON'S DISEASE

EDUARDO TOLOSA / Department of Neurology, University of Barcelona, Spain

TRAUMATIC BRAIN INJURY: A CHALLENGE FOR THE NEUROLOGIST

PIETER VOS / Dept. Neurology, Radboud University Nijmegen Medical Centre, Nijmegen The Netherlands

Traumatic Brain Injury (TBI) encompasses the functional disturbances and structural damage of the brain caused by direct impact, by external acceleration, deceleration and/or rotation forces to the head (ICD-10 classification codes S00-S09), as well as by penetrating trauma.
Pathophysiologically, TBI is characterized by diffuse damage of grey matter and white matter tracts in the brain, and by contusion, laceration and intracerebral or extracerebral haemorrhage signifying focal and/or diffuse damage (primary damage). Secondary brain injury consists of the damage that occurs in the hours-dayas post injury. Both intracranial and systemic insults (e.g. hypoxia and/or hypotension) may exacerbate secondary damage.
The incidence of TBI is high, in the international literature varying between 100 and 300 per 100,000, with the highest incidence occurring in men, aged 15 to 24 years. The average age of patients with TBI is 30 years (2). Recent data indicate an increase in average age and a larger contribution of elderly patients with TBI. Approximately 9095% of all TBIs are considered mild. Intracranial complications of mild traumatic brain injury (MTBI) are infrequent but potentially life-threatening, and may require neurosurgical intervention in a minority of cases (0.23.1%). Because of the importance to exclude the small chance of a life-threatening complication in large numbers of individual patients much research has been dedicated to the prediction of these complications.
In the presentation the diagnosis, treatment options and consequences of traumatic brain injury will be discussed.
A second topic will be how to read the CT scan with respect to relevant intracranial lesions in mild, moderate and severe TBI.
Thirdly as a special topic we will discuss traumatic axonal damage (diffuse axonal injury (DAI)) that usually results from shearing stresses on brain parenchyma, which stretch and injure axons (and or myelin) and bloodvessels, causing oedema and axoplasmic leakage. DAI is microscopic in nature and difficult or impossible to detect with CT. DAI is a white matter disorder, consisting of myelin dysfunction/ demyelination, axonal dysfunction/ injury or both. DAI causes immediate and often prolonged unconsciousness and accounts for 35% of the mortality from head injury.
Currently no accurate method is available for diagnosing and assessing the distribution and severity of diffuse axonal injury. This presentation wil also focus on the clinical

aspects of DAI, the diagnosis of DAI using MRI techniques inlcuding diffusion tensor imaging(DTI), susceptibility weighted imaging (SWI). In addition although no efficacy of any (drug) treatment has been proven untill now, some of the available evidence and the possible treatment mechanisms will be discussed.

1. Vos PE, Alekseenko Y, Battistin L, Birbamer G, Gerstenbrand F, Potapov A, et al. Mild Traumatic Brain Injury. In: Hughes RA, Brainin M, Gilhus NE, editors. European Handbook of Neurological Management. 1 ed. Blackwell Publishing; 2006
2. Vos PE, Battistin L, Birbamer G, Gerstenbrand F, Potapov A, Prevec T, et al. EFNS guideline on mild traumatic brain injury: report of an EFNS task force. Eur J Neurol 2002 May;9(3):207-19.
3. Smits M, Dippel DW, de Haan GG, Dekker HM, Vos PE, Kool DR, et al. External validation of the Canadian CT Head Rule and the New Orleans Criteria for CT scanning in patients with minor head injury. JAMA 2005 Sep 28;294(12):1519-25.
4. Vos PE, Lamers KJ, Hendriks JC, van Haaren M, Beems T, Zimmerman C, et al. Glial and neuronal proteins in serum predict outcome after severe traumatic brain injury. Neurology 2004 Apr 27;62(8):1303-10.