THE SOCIETY FOR THE STUDY OF NEUROPROTECTION AND NEUROPLASTICITY

Romanian Neurological Society

DANUBIAN NEUROLOGICAL TEACHING COURSE

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THE DANUBIAN FOUNDATION OF THE SOCIETY FOR THE STUDY OF NEUROPROTECTION AND NEUROPLASTICITY

THE UNIVERSITARY FOUNDATION 'CAROL DAVILA'

DEMENTIA SESSION

Day	Timeframe	Duration	Session / Speaker	Title
Tuesday	8:30-8:45	**15 min.**	**Opening Ceremony**	
Tuesday	8:45-9:30	**45 min.**	**Emil Toescu (UK)**	Normal and pathological brain ageing from the perspective of neuroscience
Tuesday	9:30-10:15	**45 min.**	**Vecsei Laszlo (Hungary)**	Damage of neuronal tissue: therapeutic consideration (from the biochemical point of view, mitochondrial abnormalities, kynurenine system etc.)
Tuesday	10:15-11:00	**45 min.**	**Ovidiu Bajenaru (Romania)**	Parkinson's disease associated dementia
Tuesday	11:00-11:20	20 min.	Coffee Break	
Tuesday	11:20-12:05	**45 min.**	**Antonio Federico (Italy)**	CADASIL: Clinical and molecular data of an emerging form of vascular dementia. The Siena Experience
Tuesday	12:05-12:50	**45 min.**	**Amos Korczyn (Israel)**	Could dementia be prevented through modification of vascular risk factors?
Tuesday	13:00-14:30	1h 30 min.	Lunch	
Tuesday	14:30-15:15	**45 min.**	**Bogdan Popescu (Romania)**	Genes involved in dementia
Tuesday	15:15-16:00	**45 min.**	**Dafin Muresanu (Romania)**	Pharmacological treatment of Alzheimer's disease
Tuesday	16:00-16:20	20 min.	Coffee Break	
Tuesday	16:20 17:05	**45 min.**	**Catalina Tudose (Romania)**	Non-cognitive symptoms of dementia
Tuesday	17:05-17:50	**45 min.**	**Dan Dermengiu (Romania)**	Medical and forensic implications in dementia
Tuesday	20:00	Dinner		

NEUROTRAUMA SESSION

Day	Timeframe	Duration	Session / Speaker	Title
Wednesday	9:00-9:45	**45 min.**	**Pieter E. Vos (Netherlands)**	Biochemical markers of traumatic brain injury
Wednesday	9:45-10:30	**45 min.**	**Yuri Alekseenko (Belarus)**	Early management of mild traumatic brain injury
Wednesday	10:30-10:50	20 min.	Coffee Break	
Wednesday	10:50-11:35	**45 min.**	**Klaus von Wild (Germany)**	Prediction of outcome in traumatic brain injury
Wednesday	11:35-12:20	**45 min.**	**Franz Gerstenbrand (Austria)**	Traumatic Brain Injury, biomechanic aspects and classification
Wednesday	13:00-14:30	1h 30min.	Lunch	
Wednesday	14:30-15:15	**45 min.**	**Dafin Muresanu (Romania)**	Neuroprotection and neuroplasticity in traumatic brain and spinal cord injury
Wednesday	15:15-15:30	15 min.	Coffee Break	
Wednesday	15:30-16:30	**60 min.**	**Written examination**	
Wednesday	20:00		Dinner	

THE SOCIETY FOR THE STUDY OF NEUROPROTECTION AND NEUROPLASTICITY

DEMENTIA SESSION

DAY 1 **20** March

2007, Tuesday

SPEAKERS IN ALPHABETICAL ORDER:

Bājenaru Ovidiu (Romania): Parkinson's disease associated dementia

Dermengiu Dan (Romania): Medical and forensic implications in dementia

Federico Antonio (Italy): CADASIL: Clinical and molecular data of an emerging form of vascular dementia. The Siena Experience

Korczyn Amos (Israel): Could dementia be prevented through modification of vascular risk factors?

Mureşanu Dafin (Romania): Pharmacological treatement of Alzheimer's disease

Popescu Bogdan (Romania): Genes involved in dementia

Toescu Emil (UK): Normal and pathological brain ageing from the perspective of neuroscience

Tudose Cătălina (Romania): Non-cognitive symptoms of dementia

Vecsei Laszlo (Hungary): Damage of neuronal tissue: therapeutic consideration (from the biochemical point of view: mitochondrial abnormalities, kynurenine system etc.)

Ovidiu Bajenaru

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PARKINSON's DISEASE ASSOCIATED DEMENTIA

Though considered since a long time as a pure motor disease, today it is well known that Parkinson's disease has a multilesional neurodegenerative pathology (see Braak stages I - VI) with clinical neurological signs and symptoms in multiple domains, which core is represented by the motor characteristics known as parkinsonism but accompanied by many non-motor signs and symptoms with a variable frequency: dysautonomic, sensorial, sleep disorders and psychiatric manifestations among which the cognitive impairment could progress to dementia. Parkinson's disease associated dementia (PDD) is pathologically similar to Braak's stage VI of Parkinson's disease and not different from diffuse Lewy body disease, which could be eventually diferentiated only by the clinical evolution.

PDD is present in about 40% of the patients with Parkinson's disease. Its incidence and prevalence is significantly correlated with advanced age and duration of disease, but also with other clinical characteristics as:

- motor dysability
- impaired cognitive scores
- confusion or psychotic manifestations at levodopa
- early development of hallucinations at specific drugs
- speech impairment
- axial motor impairment
- severity of bradikynesia
- depression
- decreased performance in verbal fluency tests

Among the definitory cognitive dysfunctions for dementia, the most characteristic for PDD is the dysexecutive syndrome, as usually seen also in other subcortical dementias.

The impairment of executive functions (ability in planning, organizing and controling a type of behaviour for a purposed ? aim) is the key-component of the neuropsychological deficit in Parkinson's disease (with or without dementia) and is often associated with attention impairment (with a fluctuant character as in diffuse Lewy body disease) and with memory impairment(but with a different pattern and less severe than in Alzheimer disease). In Parkinson's disease the recognition tests have better results than free evocation because the new information is retained, but the access to this information is difficult as the searching strategies are disturbed, as they are dependent on the basal ganglia circuitry; in Alzheimer disease the topography of the characteristic lesions, affecting the limbic system, determines the impairment of retention of new information mechanisms.

The dysexecutive syndrome in Parkinson's disease is clinical expressed by difficulties in creating concepts, in identifying rules, in solving problems, in elaborating and planning activities, in smooth passing from a type of activity to another, difficulties in completing a set of activities to the end. These disturbances in executive functions are different to those present in frontal cortical lesions: in Parkinson's disease there is an improved performance if the patient receives a key-element from outside, there is no disturbed attention by new stimuli and there are no errors of perseverance ?

Other clinical manifestations in PDD express as visuo-spatial disturbances which seem to be more a consequence of difficulties in sequencial organization of behaviour, which also imply the basal ganglia.

Language and praxis are less impaired than in Alzheimer disease, but a particular characteristic is that the verbal fluency is more severe disturbed in Parkinson's disease.

The behavioural and personality changes are frequent in Parkinson's disease and have the clinical appearance of organic modification of personality, characterized by more often association of depression than in Alzheimer disease and the presence of visual hallucination in more than 70% of patients, similar to diffuse Lewy body disease.

On the other side, it is also true that apart from the clinical type of PDD above described, in which the core element is the dysexecutive syndrome, in other cases there is a not infrequent independent association of Alzheimer dementia, clinically characterized by the presence of a limbic type mnestic impairment. This association is also pathologically supported by studies showing the coexistence of Lewy bodies with senile plaques and neurofibrillary tangles; a possible explanation of this association could be the age related correlation of both diseases.

There is another series of studies suggesting correlations among the different neurochemical changes and clinical manifestations of PDD. There are correlative data between dopaminergic decreased activity and the dysexecutive syndrome (at least partially), cholinergic decreased activity and mnestic and attention disorders, noradrenergic decreased activity and partially attention impairment, decreased serotoninergic activity and the depressive disposition.

Associating all these data, we could assume that the diffuse Lewy body type pathology (or maybe more specifically, α-synucleinopathy type), is the cause of PDD and also of the cortical (particulary with impairment of temporal neocortex) and limbic forms of diffuse Lewy body disease, independent or additive to an Alzheimer type pathology. In these conditions we could affirm that Parkinson's disease and Alzheimer disease are the extremes of a spectrum of neurodegenerative diseases, which most often are intricated and reflect common pathogenic mechanisms (abnormalities in expression and/ or processing some cellular Proteins) affecting specific vulnerable cell populations in CNS.

As long as neurochemically the cholinergic deficit is constantly associated with cognitive impairment also in PDD, the clinical trials have started from the supposition that cholinesterase inhibitors, clinically proved to be efficient in Alzheimer disease could also have benefits in PDD. More preliminarry trials, followed by the results of EXPRESS trial have shown that these drugs, in particular rivastigmine, have moderate

but significant improvement in this type of dementia, both through the results of global evaluation scores and of cognitive function scores (including the executive functions and attention), and also of behavioural scores, at the same magnitude as in Alzheimer dementia. These data reccomend today the administration of cholinesterase inhibitors, in particular rivastigmine, for the parkinsonian patients associating dementia and discourrage the use of anticholinergics as antiparkinsonian agents in patients with cognitive impairment, with or without dementia.

BIBLIOGRAPHY (selective)

1. Cummings JL. - Intellectual impairment in Parkinson's disease: clinical, pathologic, and biochemical correlates. J Geriatr Psychiatry Neurol 1988;1:24-36.
2. Emre M. - Dementia associated with Parkinson's disease. Lancet Neurol 2003; 2: 229-37.
3. McKeith I, Mintzer J, Aarsland D, et al.- Dementia with Lewy bodies. Lancet Neurol 2004;3:19-28.
4. Braak H, Del Tredici K, Rub U, de Vos, RA, Jansen Steur EN, Braak E. - Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol Aging 2003; 24:197-211.
5. Perry EK, Curtis M, Dick DJ, et al. - Cholinergic correlates of cognitive impairment in Parkinson's disease: comparison with Alzheimer's disease. J Neurol Neurosurg Psychiatry 1985;48:413-21.
6. Tiraboschi P, Hansen LA, Alford M, et al. - Cholinergic dysfunction in diseases with Lewy bodies. Neurology 2000;54:407-11.
7. Bohnen NI, Kaufer DI, Ivanco LS, et al.- Cortical cholinergic function is more severely affected in parkinsonian dementia than in Alzheimer disease: an in vivo positron emission tomographic study. Arch Neurol 2003; 60:1745-8.
8. McKeith I, Del Ser T, Spano P-F, et al.- Efficacy of rivastigmine in dementia with Lewy bodies: a randomised, double blind, placebo-controlled international study. Lancet 2000; 356:2031-6.
9. Reading PJ, Luce AK, McKeith IG. Rivastigmine in the treatment of parkinsonian psychosis and cognitive impairment: preliminary findings from an open trial. Mov Disord 2001;16:1171-4.
10. Aarsland D, Laake K, Larsen JP, Janvin C.- Donepezil for cognitive impairment in Parkinson's disease: a randomised controlled study. J Neurol Neurosurg Psychiatry 2002; 72:708-12. [Erratum, J Neurol Neurosurg Psychiatry 2002;73:354.]
11. Giladi N, Shabtai H, Gurevich T, Benbunan B, Anca M, Korczyn AD. Rivastigmine (Exelon) for dementia in patients with Parkinson's disease. Acta Neurol Scand 2003;108:368-73.
12. Clegg A, Bryant J, Nicholson T, et al.- Clinical and cost-effectiveness of donepezil, rivastigmine and galantamine for Alzheimer's disease: a rapid and systematic review. Health Technol Assess 2001;5:1-137.
13. Doody RS, Stevens JC, Beck C, et al.- Practice parameter: management of dementia (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2001;56:1154-66.
14. Huber SJ, Paulson GW, Shuttleworth EC.- Relationship of motor symptoms, intellectual impairment, and depression in Parkinson's disease. J Neurol Neurosurg Psychiatry 1988;51:855-8.

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MEDICAL AND FORENSIC IMPLICATIONS IN DEMENTIA

In Romania the activity of expert appraisal tangential to psychiatry is carried on within the network of forensic medicine, under the name of forensic psychiatric expert appraisal, having a mixed theoretical basis, a psychiatric one - analytical, and a forensic one - causal, thus representing, theoretically speaking, more than "legal psychiatry" as it is commonly called. The bases of this direction were laid by the psychiatrist Alexandru Sutu, but the applied and legal theoretical foundation remained with Mina Minovici, whose published cases represent models of interdisciplinary expert appraisals even nowadays.

The psychiatric medical - legal activity, through the domains of expert appraisals, research and assistance aiming at the category of persons with judicial involvements:

- Its object of activity is the healthy or the mentally ill person, as against the social norms established by the instruments of the lawful state, who has to find himself/herself, in agreement with the others in a given setting (while general psychiatry deals with the ill person who reports to himself/herself, in a given social setting);
- It analyses the whole and interprets synthetically the medical and non-medical findings according to the principles of forensic causality;
- It synthesizes all the information (involving other medical and non-medical approaches as well, and it interprets their cause). This synthesis becomes a conclusive document necessary for justice.

Forensic activity, including psychiatric forensic activity is regulated by law, government decision, codes of procedure, its methodology being very strict.

Thus, based on a beneficial tradition, legally statutory for more than a century, the activity of legal psychiatry is carried on within the network of forensic medicine, by interdisciplinary boards led by a forensic doctor, the members being psychiatrists. The expert appraisals are performed on the basis of a written order, issued by one of the institutions qualified by law to request forensic reports. The forensic doctor, due to his training, represents the interface, the optimum rationale, synthetic connection between the psychiatrist whose duty is to perform a psychiatric examination and to reconstitute the psychiatric status prior to the date of the examination and the institutions appointed by law to request the determination of the mental capacity.

The roles, within the activity of legal psychiatry, appear now even more clearly defined: the lawyer evaluates "the guilty will", the "absence of the capacity of free will" etc., the psychiatrist evaluates the cognitive - affective capacity, and implicitly the volatile capacity, the forensic specialist analyses the forensic causal system, and the psychiatrist specialized in legal psychiatry analyzes the global mental capacity to use free will, to understand the requirements and the constraints to which he/she has to be submitted and his/her motivational system, in order to include him/her in the norms of the justice system. Within the interdisciplinary team, the last two specialists evaluate, according to forensic causal principles, the capacity of the person to understand the contents and the negative social consequences resulting from his/her unlawful acts (which are considered or not to be the expression of a free will) and gives an opinion in criminal cases about the degree of the social danger and of the necessary medical measures. In civil cases, the interdisciplinary board gives an opinion on the mental capacity. The conclusions of a forensic psychiatric expert's report scientifically endorsed provide the requesting institutions the necessary medical criteria for analyzing the criminal responsibility or civil fitness of a person at the time when he/she caused an event stipulated by criminal or civil law.According to the law, only the forensic boards stipulated by law can make a decision on the above.

The theoretical bases of this approach start from the axiom according to which any forensic appraisal, including a psychiatric one, should not be mistaken for a diagnosis, as it represents a scientific report which provides to the justice system a complex, dynamic interpretation of a situation, of a behavior which resulted in an event stipulated by the criminal code or by the civil code. The analytical mechanism of approach, specific for legal psychiatry, aims at the existential race of the person, the relations between the person and the world, the mental status prior to the event, at the time of the commission of the act, afterwards and at the time of the examination, the synthesis of the intention and the concrete synthesis of all the acts, the phenomenological reduction in order to obtain the truth values, the analysis of the presence and co-presence of the elements possibly or actually involved, the forensic causality. This model of interdisciplinary approach leads to the necessary phenomenological reduction for the corroboration of the data regarding the circumstances in which the event occurred due to which justice had to be brought in.

The medical and forensic relationships of psycho-organic pathology comprise the whole range of specific activities. Criminal cases and cases when there is a need to interrupt or postpone the penalty are easier to solve because the judicial implications are clearer and the inter-departmental and inter-disciplinary relationships are narrower; in civil cases the activity is more difficult especially due to a widening of the inter-disciplinary area and the passionate involvement of the parties, as material goods are involved.

In forensic psychiatry we use the terms of psychiatric capacity and mental fitness, the state of awareness being a must, but not enough to evaluate the wholeness of mental capacity.

Thus, in civil cases, the capacity of civil fitness is defined as a person's mental capacity to understand the content and especially the consequences of a unilateral civil document (wills) or bilateral ones (contracts, etc.). The state of mental normality or abnormality (the underlying condition), or particular transitory or comprehensible states are taken into account. In other cases, irrespective of the degree by which the mental capacity is diminished, or even absent, the capacity of mental fitness, a phrase which is synonymous to mental fitness in criminal cases, is absent (missing) because it is logical that in a court of law the validity of a signature cannot be graded. In these cases as well, the mental capacity is retrospectively assessed by reconstructing the mental state at

a time prior to the examination or "on paper" examination. A special situation is present which requires the annulment of a dead person's signature when the forensic reports "on the documents" involve a complete, accurate medical evaluation of the documents in order to be able to analyze the pathoplastic biological background that could lead to a mental disease, being attributed to medical and non medical evidence.

In the other civil cases, the mental capacity at the time of the report with a predictive value for the foreseeable or non foreseeable future is assessed. In these cases we take into consideration the mental capacity to decide (decisional capacity) with free will about oneself or others (to decide on the way "to be" in relation to the legal civil rights and duties granted by the legal rules). Such examples are restraining orders, child care, adoptions, sexual identity, etc.

A special case is when a person claims civil damages on the grounds of a disease caused by another natural or legal person. Very often, claims for damages for physical trauma (accidents, fights), inadequate medical treatment or in hospital deaths fall into this category. In such cases, we operate with concepts of medical and legal causality, mental medical and legal causality and mental disability.

In medical and legal psychiatry, conclusions are drawn more on the basis of symptoms rather than on the underlying condition.

Most symptoms refer to mental functions such as willingness and simulation, which are considered as secondary or irrelevant in hospital practice.

In civil cases, forensic medicine has to demonstrate the (in/)existence of the possibility to exhibit (display) one's free will at some point, involving a comprehensible or incomprehensible motivational background. As in all human activities, errors may occur and these can have either organizational or methodological causes, with both objective and subjective elements involved.

Psychiatric medical and legal errors occurring in psycho organic pathology dementia types can be classified as errors of taxonomic, organizational origin which involve the interdisciplinary collaboration of medical and legal psychiatry/neurology/paraclinical specialities. These errors are the basis of the other types of errors.

According to the WHO international classification of diseases, dementias are classified in chapter V, mental and behavioral diseases, codes F00/ F09 and in the class of neurological diseases, codes G 30, G 31.1. and G 31.2 regarding degenerative disorders of the nervous system. For reasons which cannot be discussed within forensic medicine, other types of dementia are not discussed. This is why medical and legal difficulties arise especially concerning these nosologic classification.

The coding of degenerative dementias in both groups has to be accepted in the following way:

1. The neurologist does not have the competence to express his opinion on a person's mental capacity even if he or she has been diagnosed with dementia.
2. A person goes first to a psychiatrist or a neurologist.
3. If the patient goes to the neurologist first, the doctor determines the neurologic diagnosis as main diagnosis, secondary diagnosis and comorbidity.
4. Dementia is seldom the main diagnosis.
5. In order to diagnose dementia within degenerative diseases of the nervous system, irrespective of its written ranking, it is necessary to emphasize specific criteria for both neurological and psychiatric diagnosis, as well as specific mental examination.
6. The patient may refuse a psychiatric examination and under thes circumstances the neurologist's responsibility becomes greater, as he has to mention this fact. The neurologist's statement has to be signed by the patient's family as well.
7. Laboratory tests are compulsory under these circumstances. Forensic medicine considers as compulsory the support of electro physiological computerized and imaging complementary exams for the diagnosis of degenerative diseases.
8. Forensic medicine does not dismiss a priori the diagnosis of dementia put by a neurologist, especially if there is the support of complementary exams, and considers that the stages can be recognized by any experienced physician, but it recommends the inclusion of critical symptoms for the out patient visits.
9. If the patient goes first to the psychiatrist, the doctor determines a multi axial diagnosis, on the diagnosis axis I being included dementia and on the axis III the associated organic pathology which is confirmed by an interdisciplinary examination and suitable paraclinical investigations. It is the psychiatrist's duty to establish the stage of the disease.

By observing the above mentioned activity parameters, neither group of specialists can be blamed for malpraxis. They offer the psychiatric medical and forensic boards at the same time a real clinical picture which can be associated with non medical evidence in order to assess the mental capacity of the patient concerning the criminal or civil case in which the latter is involved.

Whereas in psychiatric forensic expert appraisals the actual physical examination of a person is easier (due to the fact that boards have the legal right to require the medical examinations that are considered necessary, including hospital admission, and the public health network is legally bound to fulfill such requirements), in expert appraisals based on documents the situation is more complicated.

These expert appraisals are commonly performed in order to establish a dead person's mental capacity at the time when he/she had a civil document drawn up which is contested by third parties. Large fortunes are generally at stake. In such expert appraisals, the person's mental capacity to manifest oneself with free will at the time the civil document under litigation was drawn up is assessed. Implicitly, this involves a critical assessment of the legal and social consequences following that document. Under these circumstances, the forensic institution is tributary to the professional quality of the medical tests that have been performed and corroborated with the non medical evidence.

Forensic institutions are the only medical institutions which use, for medical and forensic work, non medical evidence.

The failure to corroborate medical and non medical data, as well as incomplete data, are the most frequent underlying causes for errors in setting the medical criteria necessary for the justice system.

The medical issue under discussion includes the nosologic classification, the symptoms that can be reconstructed for the time the expert must state his opinion regarding the document that was drawn up, the reconstruction of the motivational system and, finally, their association as underlying patterns of willingness capacity. In order for a civil document to be considered as having been drawn up with the observation of the legal norms and common sense principles: it must not be seriously detrimental to one party, not to have been obtained by fraud, and all the parties involved must have had their mental capacities. For people with a pathology which required an expert appraisal, the comprehensibility of the motivation and the absence of manipulation through volitional deficit have to be demonstrated.

As a matter of fact, within psycho organic syndromes, dementia syndromes included, the difficulty arises concerning the onset, especially for primary dementia.

Subcortical dementias, through the damage of the subcortical structures, especially the thalamus, and of the subcortical frontal connexions, are difficult to

diagnose at onset. This is exactly at the time when the least visible behavioral changes occur, with a deficit to formulate strategies and to process new information.

In degenerative dementias with a slow onset through behavioral and affectivity changes, difficulties arise from the facade which is maintained for a longer period of time with apparently unchanged adaptability. In such cases, there are regularly mismatches among the non medical pieces of evidence , especially regarding the cognition apparently preserved. The detailed psychiatric examination is the main source for the data necessary to differentiate from pseudo dementias, depressive pathology or vascular clinical pictures.

I am going to illustrate this with a case referred to the National Institute for Forensic Medicine by one of the well known teaching centers. The patient was a female with a psycho traumatic life experience, well educated, without children. She left her workplace and shortly afterwards she drew up a civil document, being at the same time robbed of some money. She went on a trip and when she returned she was admitted to hospital, where a state of the art medical file was drawn up: detailed mental examination, special social enquiry performed by the staff of the psychiatric system, psychological examination, electro physiological and imaging investigations, neurological and medical examinations. The diagnosis was unanimous: Alzheimer's dementia, first stage. Detailed notes were kept on a permanent basis. Death followed shortly. After the patient's death, the family learned about the civil document and contested it. At the NIFM, the medical documents and especially the social enquiry, corroborated with the non medical evidence, proved that at the time when the document was signed, the person exhibited the early signs of Alzheimer's disease (concerning especially the progressive loss of the ability to use one's own experience, the progressive deficit in the individual adaptative ability, with an onset prior to the drawing up of the document, and the first signs of inconstant spatial disorientation). If the medical file had not been detailed, if there had not been a social enquiry which is not regularly performed, it would have been impossible to present arguments and counter arguments only on the basis of the evidence. A favorable circumstance in such difficult cases is also the fact that lawyers do not know about ICD 10 DCR and refer ony to DSM, ICD 1 and textbooks when they ask us to explain why we support the absence of mental capacity once Alzheimer's disease and not dementia was diagnosed and to explain what was involved in diminishing the mental capacity. Also in connection with Alzheimer's dementia I would like to make a further point concerning prudence. As a forensic specialist, I consider that the most accurate diagnosis is made by autopsy. One patient was neurologically diagnosed in an out patient clinic on the basis of a check up in the out patient clinic and of an imaging examination, as having dementia. The neurologist correctly recommended the patient to be admitted in a psychiatric unit, which did not happen because of the patient's family lack of involvement. Thus, post mortem, forensic medicine specialists were involved. The first board made the diagnosis of Alzheimer's dementia on the basis of a CT scan. Only through thorough corroboration of non medical evidence with the neurologist's examination report could the specialists at the NIFM diagnose mixed dementia. Both the neurologist who failed to write down the critical symptoms, and the mixed board which used only a CT scan to diagnose the type of dementia were careless (imprudent).

As far as Pick disease is concerned, the psychiatric forensic actions are easier in the case of onset with strange childish behavioral and affectivity patterns but more difficult in the case of onset with an asthenic syndrome. In vascular and senile dementias affective instability, changes in behavior, the involvement of stressful events and even early cognitive changes can be reconstructed. As far as these dementias are concerned, the difficulties arise from interdisciplinary collaboration. These patients are regularly admitted in internal medicine departments, which do not ask for a neurologic examination since there is no vascular stroke as yet, nor do they ask for a psychiatric examination because the patient exhibits awareness.

Another quite delicate issue arises from modern therapy. From our observations, we can state that neurological vascular pathology, if treated correctly, does not cause changes in the mental capacity in all patients.

The problems are quite different for patients with Alzheimer's disease who receive modern treatment. We have repeatedly emphasized the fact that even if there are spectacular improvements as far as adaptability and even cognition are concerned, this does not apply to the volitional background. Under treatment with aricept or exelon, patients who give the impression that their behavior is normal or do not have cognition deficits, are left without home or money through manipulation. In such cases, the corroboration of all the pieces of evidence is not only compulsory, but also necessary.

To sum up, the problems of dementias involved in legal cases are dominated by the onset of the disease, by the evolution under treatment and by the beneficial collaboration between neurology and psychiatry and between the two and forensic medicine, with the observance of competencies and of the norms for drawing up the medical documents.

As a result of the previous points made, we would like to emphasize the following:

1. Forensic medicine cannot allow for errors which have legal consequences and, thus it must point out possible sources of errors.
2. In forensic practice concerning the psycho organic pathology of dementia type, it is necessary to closely follow the mixed, psychiatric and neurological, criteria patterns for the diagnosis, including a minimum of paraclinical investigations, such as psychological examination, computerized EEG and CT scan.
3. The interdisciplinary collaboration between neurology, psychiatry and forensic medicine becomes an essential requirement in order to prevent possible judicial errors.

BIBLIOGRAPHY:

1. Costea Gabriela (1995), Proposals for Updating the Activity of Forensic Physchiatric Expert Appraisals, the Romanian Journal of Legal Medicine, 3,(4) 396-400.
2. Dermengiu D. (2002), Forensic Pathology, Edit. Romanian Medical Life
3. Dragomirescu V., Scripcaru G., (1997), Analytical Overview on the Current Methodological Organization of Forensic Expert Appraisal, Paper Delivered at the National Meeting of Forensic Psychiatry Medicine, 26 27 Sept., Bucharest;
4. Dragomirescu V., Hanganu O., Prelipceanu D., (1990), Forensic Psychiatric Expert Appraisal, the Medical Publishing House, Bucharest

** Papers of the Colloquim Regarding Responsibility and Psychiatric Treatment (1986), the European Committee on Criminal Matters by the Council of Europe, Strasbourg;

** Principles Regarding the Protection of Patients with Mental Diseases for the Improvement of Mental Health, (1991), Un;

** Principles Regarding the Protection of People with Mental Diseases for the Improvement of Mental Health, (1991), Un;

THE SOCIETY FOR THE STUDY OF
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CADASIL: CLINICAL AND MOLECULAR DATA OF AN EMERGING FORM OF VASCULAR DEMENTIA. THE SIENA EXPERIENCE

Abstract

CADASIL (cerebral autosomal dominant arteriopathy with subcortical infartcs and leuokoencephalopathy) is an inherited cerebrovascular disease due to mutations of the Notch3 gene at the chromosome locus 19p13. The clinical spectrum includes recurrent ischemic episodes, cognitive deficits, migraine and psychiatric disorders. The histopathological hallmark of CADASIL is accumulation of electron dense granules (GOM) in the media of arterioles. MRI reveals extensive cerebral with matter lesions and subcortical infartcs. CADASIL was initially thought to be a rare disorder, but increasing number of families have been identified; therefore, it is likely that CADASIL is still largely underdiagnosed.
Here we report an update on mutations of Notch3 gene and some information on the pathogenesis of the disease.

Introduction

The understanding of the pathogenesis of strokes in the recent years has been highly improved, and many molecular genetic conditions have been found related with this symptom. Between them, CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leucoencephalopathy; OMIN 12310), firstly described by Tournier-Lasserve et al (1) receives a strong interest for its clinical heterogeneity, inheritance and frequency.

Clinical Aspects

CADASIL is an autosomal dominant vascular disorder, clinically characterized by a variety of symptoms including migraine with aura, mood disorders, recurrent subcortical ischemic strokes, progressive cognitive decline, dementia and premature death. The vascular lesions underlying CADASIL are a non arteriosclerotic, non amyloid arteriopathy affecting primarily small cerebral arteries, although the vascular defects are present in every tissue and may be detected histologically by examining arterioles in skin biopsy, where accumulation of granular and osmiophilic material within the smooth muscle cell basement membrane and the surrounding extracellular matrix have been reported.
MRI is characterized by hyperintense lesions on T2-weighted images in the subcortical white matter and basal ganglia. Skehan et al. studied the MRI appearance in 10 individuals in one large Irish autosomal dominant family and found 2 major types of abnormalities. The most striking were large confluent patches of high-signal change on T2- and proton density-weighted images present throughout the white matter, especially in the anterior part of the temporal lobes and the periventricular portion of the occipital lobes. Additionally, they detected small linear and punctate lacunes present not only in the periventricular white matter but also in the brain stem, basal ganglia, thalamus, external capsule, and corpus callosum (2) (Fig.1).
More recently Lesnik Oberstein et al. describing an increase in white matter hyperintensities on brain MRI compared to controls., confirmed that the characteristic patterns of lesions is located in the anterior temporal lobes, the frontal lobes and the periventricular caps (3).
The course of the disease is very heterogeneous, even in the same family; some patients remain asymptomatic until their seventies, whereas others are severely affected since the age of 50. A description of the clinical phenotype has been reported by Dichgans et al (4).

Molecular genetics

CADASIL is caused by mutations in the NOTCH3 gene (5). Notch 3 is one of four mammalian homologous of Drosophila Notch. Notch genes code for large transmembrane receptors involved into cell fate decision during embryonic development. The Notch 3 receptor is proteolytically processed in the trans-Golgi network as it traffics from the endoplasmatic reticulum to the plasma membrane. Proteolytic cleavage results in a large extracellular fragment and a small intracellular fragment that contains the tramsmembrane region (fig. 2A). Interaction of Notch receptor with its ligand leads to cleavage of the transmembrane receptor which migrates into the nucleus and, associated with a transcription factor, activates transcription of primary target genes (Fig.2B).
Like all Notch receptors, Notch 3 contains a large number of tandemly arranged epidermal growth factor-like (EGF-like) repeat domains, which account for most of the extracellular part of protein. The gene consists of 34 exons, all of them virtually may have pathogenetic mutations (Fig 3).
Numerous mutations have been in the recent years described in this gene, giving to the disease a large genetic heterogeneity. Until now, no genotype-phenotype relationship has been described.
All CADASIL-related mutations occur in exons that encodes one of the 34 EGF-repeat domains. To date, about 100 different mutations in Notch3 gene have been reported in CADASIL patients, the 95% being missense point mutations (Fig. 4). The remaining consists of five little deletions (four in frame and one frame shift) and one splice site mutation. Many polymorphisms have also been identified in the Notch3 coding sequence. All mutations (except two missense mutations and one deletion) result in an odd number of cysteine residues, suggesting the occurence of abnormal disulfide bridging and protein misfolding. These would cause changes in receptor activation and abnormal signal transduction. Having said that though, the mechanism by which CADASIL mutations become pathogenic are actually unknown.

Spectrum of mutations in CADASIL

The low sensitivity of skin biopsy for diagnosis of CADASIL, reported by Markus et al (6). and also in our experience give to the molecular genetic approach the diagnostic key of this disorder. However, the length of the gene (34 exons) is one of limitation for a complete gene sequencing for its time and money cost. Since the article of Joutel et al (7) and more recently of Markus (8?), it has been reported that most mutations were located in exon 4, followed by exon 3, 5 and 6, and 8, 18 and 22, based on experience on 48 index patients. Lesnik Oberstein (9) reported his experience in Ducht families, confirming the high exon 4 mutation frequency, but the second highest frequency of mutations has been found in exon 11, and then exons 5,6 and 19, suggesting a variation in mutational spectrum between CADASIL populations. Similar geographic variations have been described also in Italy, with an higher frequency of exon 3 and 4 mutations in the north, of exons 4 and 11 in the centre and of 8 in the south (10).

All the known missense mutations in Notch3 linked to CADASIL are reported in table I and clearly indicate the genetic heterogeneity of the disease. Table II shows deletions and table III the polymorphisms in Notch 3 coding sequence.
Fig 3 reports the number of mutations in each exon, indicating the higher number of mutations found in exon 4, followed by exons 8, 3, 5, 11, 19, 18, 2, 6, 10, 20, 7, 9, 14, 22 and 23.

Conclusions

CADASIL is one of the new diseases that concentrate the interest of neurologists for its frequency, for the clinical heterogeneity, for their inheritance (but also sporadic cases have been reported and even in childhood) for the possibility of a diagnostic confirmation only on molecular genetic basis. The very long list of mutations here described gives to the clinicians an idea about the complexity of the problem and suggests them to avoid to consider the exclusion of the diagnostic hypothesis of CADASIL only after all the gene has been analyzed. In a recent articles that will appear in the next months, we have found a regional differences in the mutations from the North and the South of Italy, suggesting the existence of a regional cluster of mutations that may facilitate the diagnostic screening (10).
This is also a first contribution to collect mutations for the different neurological disorders, that will be periodically updated.

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References

1. Tournier-Lasserve E, Iba-Zizen MT, Romero N, Bousser MG (1991) Autosomal dominant syndrome with stroke-like episodes and leukoencephalopathy. Stroke 22: 1297-1302

2. Skehan SJ, Hutchinson M, MacErlaine DP (1995) Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy: MR findings. Am J Neurorad 16: 2115-2119

3. Lesnik Oberstein SAJ, van den Boom R, Middelkoop, HAM, Ferrari MD, Knaap YM, van Houwelingen HC, Breuning MH, van Buchem MA, Haan J (2003) Incipient CADASIL. Arch Neurol 60: 707-712

4. Dichgans M, Mayer M, Uttner I, Bruning R, Muller-Hocker J, Rungger G, Ebke M, Klockgether T, Gasser T (1998) The phenotypic spectrum of CADASIL: clinical findings in 102 cases. Ann Neurol 44: 731-739

5. Joutel A, Corpechot C, Ducros A, Vahedi E, Chabriat H, Mouton P, Alamowitch S, Domenga V, Cécillon M, Maréchal E, Maciazek J, Vayssiere C, Cruaud C, Cabanis EA, Ruchoux MM, Weissenbach J, Bach JF, Bousser MG, Tournier-Lasserve E (1996) Notch 3 mutations in CADASIL, a hereditary adult-onset condition causing stroke and dementia. Nature 383, 707-710

6. Markus HS, Martin RJ, Simpson MA, Dong YB, Ali N, Crosby AH, Powell JF (2002) Diagnostic strategies in CADASIL. Neurology 59: 1134-1138

7. Joutel A, Vahedi K, Corpechot C, Troesch A, Chabriat H, Vayssiere C, Cruaud C, Maciazek J, Weissenbach J, Bousser MG, Bach JF, Tournier-Lasserve E (1997) Strong clustering and stereotyped nature of Notch3 mutations in CADASIL patients. Lancet 350: 1511-1515

8. Markus HS (2003) Diagnostic strategy of CADASIL. Neurology 60: 220

9. Lesnik Oberstein SAJ (2003) Diagnostic strategy in CADASIL. Neurology 60: 2019-2020

10. Dotti MT, Federico A, Mazzei R, Bianchi S, Scali O, Conforti FL, Sprovieri T, Guidetti D, Aguglia U, Consoli D, Pantoni L, Sarti C, Inzitari D, Quattrone A. The spectrum of Notch3 mutations in 28 Italian CADASIL families. J Neurol Neurosurg Psychiatry (in press)

11. Escary JL, Cécillon M, Maciazek J, Lathrop M, Tournier-Lasserve E, Joutel A (2000) Evaluation of DHPLC analysis in mutational scanning of Noth3, a gene with a high G-C content. Hum Mut 16:518-526

12. Moon SY, Kim HY, Seok JI, Kwon JC, Ki CS, Kim JW, Suh YL, Na DL (2003) A novel mutation (C67Y) in the Notch3 gene in a korean CADASIl patient. J Korean Med Sci 18(1):141-144

13. Kalimo H, Ruchoux MM, Viitanen M, Kalaria RN (2002) CADASIL: a common form of hereditary arteriopathy causing brain infarcts and dementia. Brain Pathol 12:371-384

14. Dichgans M, Ludwig H, Müller-Höcker J, Messerschmidt A, Gasser T (2000) Small in-frame deletions and missense mutations in CADASIL: 3D models predict misfolding of Notch3 EGF-like repeat domains. Eur J Hum Genet 8:280-285

15. Wang ZX, Lu H, Zhang Y, Bu DF, Niu XY, Zhang Z, Huang YN, Yuan Y (2004) NOTCH3 gene mutations in four Chinese families with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. Zhonghua Yi Xue Za Zhi 84:1175-1180

16. Rojas-Marcos I, Encarnacion M, Martinez-Yelamos S, Ferrer I, Arbizu T,

Gil-Peralta A, Garcia-Lozano JR (2004) Gene symbol: NOTCH3. Disease: CADASIL. Hum Genet 115:175

17. Joutel A, Favrole P, Labauge P, Chabriat H, Lescoat C, Andreux F, Domenga V, Cécillon M, Vahedi K, Ducros A, Cave-Riant F, Bousser MG, Tournier-Lasserve E (2001) Skin biopsy immunostaining with a Notch3 monoclonal antibody for CADASIL diagnosis. Lancet 358:2049-2051

18. Grigg R, Lea R, Sullivan AA, Curtain R, MacMillan J, Griffiths L (2000) Identification of a novel mutation C144F in the Notch3 gene in an Australian CADASIL pedigree. Hum Mut: Mutation and polymorphism report #176 Online

19. Malandrini A, Albani F, Palmeri S, Fattapposta F, Gambelli S, Berti G, Bracco A, Tammaro A, Calzavara S, Villanova M, Ferrari M, Rossi A, Carrera P (2002) Asymptomatic cores and paracrystalline mitochondrial inclusions in CADASIL. Neurology 59:617-620

20. Santa Y, Uyama E, Chui DH, Arima M, Kotorii S, Takahashi K, Tabira T (2003) Genetic, clinical and pathological studies of CADASIL in Japan: a partial contribution of Notch3 mutations and implications of smooth muscle cell degeneration for the pathogenesis. J Neurol Sci 212:79-84

21. Yamada H, Yasuda T, Kotorii S, Takahashi K, Tabira T, Sunada Y (2001) Report of a patient with CADASIL having a nivel missenso mutation of the Notch3 gene-association with alopecea and lumbar herniated disk. Rinsho Shinkeigaku 41:144-146

22. Matsumoto H, Tsumoto M, Yamamoto T, Takahashi K, Tabira T, Ugawa Y, Tsuji S (2005) A case of early stage CADASIL showing only dizziness and vertigo with a novel mutation of Notch3 gene. Rinsho Shinkeigaku 45:27-31

23. Lesnik Oberstein SAJ, Ferrari MD, Bakker E, van Geisel J, Knoppers ALJ, Frants RR, Breuning MH, Haan J (1999) Diagnostic Notch3 sequence analysis in CADASIL: three new mutations in Dutch patients. Neurology. 52:1913-1915

24. Kotorii S, Takahashi K, Kamimura K, Nishio T, Arima K, Yasuda H, Uyama E, Uchino M, Sueyaga A, Matsumoto M, Kuchel G, Rouleau GA, Tabira T (2001) Mutations of the Notch3 gene in non-caucasian patients with suspected CADASIL syndrome. Dement Geriatr Cogn Disord 12:185-193

25. Azzarelli B, Miravalle L, Olson J, Ghetti B, Biller J, Vidal R (2003) CADASIL: a familial form of cerebrovascular disease leading to dementia. Identification of two new families and a novel mutation. Neurology 60 (Suppl1): A368

26. Oliveri RL, Muglia M, De Stefano N, Mazzei R, Labate A, Conforti FL, Patitucci A, Gabriele AL, Tagarelli G, Magariello A, Zappia M, Gambardella A, Federico A, Quattrone A (2001) A novel mutation in the Notch3 gene in an Italian family with cerebral autosomal arteriopathy with subcortical infarcts and leukoencephalopathy. Arch Neurol 58:1418-1422

27. Thomas NJ, Morris CM, Scaravilli F, Johansson J, Rossor M, De Lange R, St Clair D, Nicoll J, Blank C, Coulthard A, Bushby K, Ince PG, Burn D, Kalaria RN (2000) Hereditary vascular dementia linked to Notch3 mutations: CADASIL in British families. Ann N Y Acad Sci 903:293-298

28. Arboleda-Velasquez JF, Lopera F, Lopez E, Frosch MP, Sepulveda-Falla D, Gutierrez JE, Vargas S, Medina M, Martinez de Arrieta C, Lebo RV, Slaugenhaupt SA, Betensky RA, Villegas A, Arcos-Burgos M, Rivera D, Restrepo JC, Kosik KS (2002) C455R notch3 mutation in a Colombian CADASIL kindred with early onset of stroke. Neurology 59:277-279

29. Mazzei R, Conforti FL, Lanza PL, Sprovieri T, Lupo MR, Gallo O, Patitucci A, Magariello A, Caracciolo M, Gabriele AL, Fera F, Valentino P, Bono F, Cenacchi G, Santoro G, Muglia M, Quattrone A (2004) A novel Notch3 gene mutation not involving a cysteine residue in an Italian family with CADASIL. Neurology 63:561-564

30. Joutel A, Chabriat H, Vahedi K, Domenga V, Vayssiere C, Ruchoux MM, Lucas C, Leys D, Bousser MG, Tournier-Lasserve E (2000) Splice site mutation causing a seven amino acid Notch3 in-frame deletion in CADASIL. Neurology 54:1874-1875

31. Dotti MT, De Stefano N, Bianchi S, Malandrini A, Battisti C, Cardaioli E, Federico A (2004) A novel NOTCH3 frameshift deletion and mitochondrial abnormalities in a patient with CADASIL. Arch Neurol 61:942-945

32. Dichgans M, Herzog J, Gasser T (2001) Notch3 mutation involving three cysteine residues in a family with typical CADASIL. Neurology 57:1714-1717

33. Dong Y, Hassan A, Zhang Z, Huber D, Dalageorgou C, Markus HS (2003) Yield of screening for CADASIL mutations in lacunar stroke leukoaraiosis. Stroke 34:205-206

Figure Legends

Fig. 1: MRI in CADASIL at different stage of the disease.

Fig. 2a: Maturation of the Notch3 receptor

Fig. 2b: Simplified overview of Notch signalling in mammals

Fig. 3: Notch3 predicted protein structure
EGF-like repeat domains: extracellular domain containing 34 tandemly arranged EGF-like repeats
LNR: 3 cysteine-rich Notch/Lin-12 repeats
TM: transmembrane region
Ankyrin: intracellular domain containing 6 ankyrin repeats

Fig. 4: Summarizing graphic of mutations identified in the Notch3 gene

Fig. 1

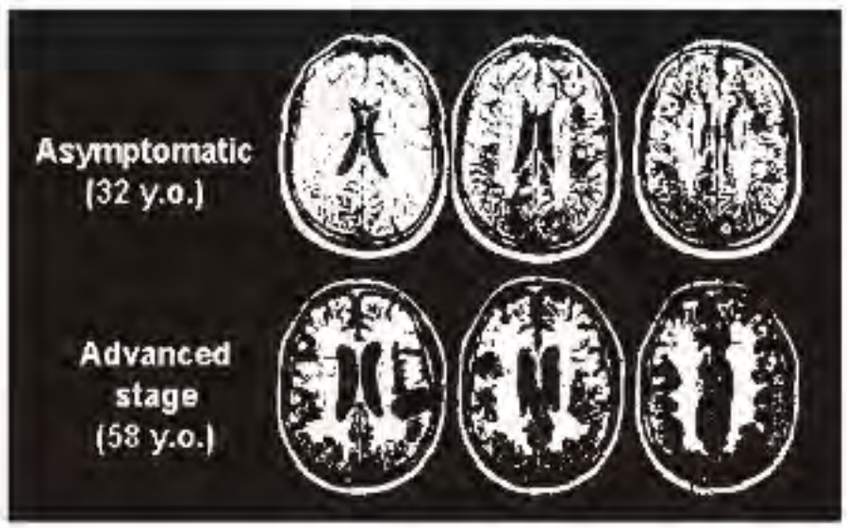
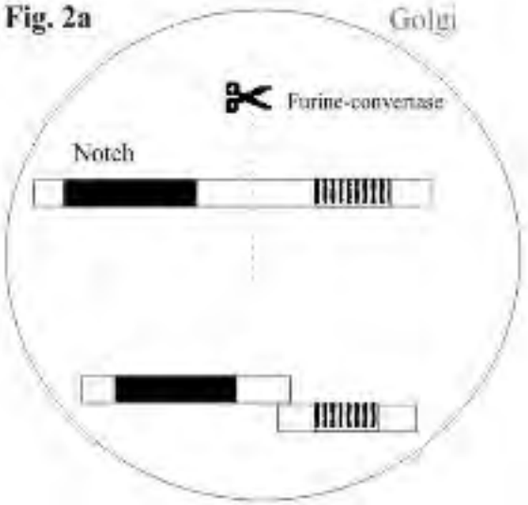


Fig. 2a



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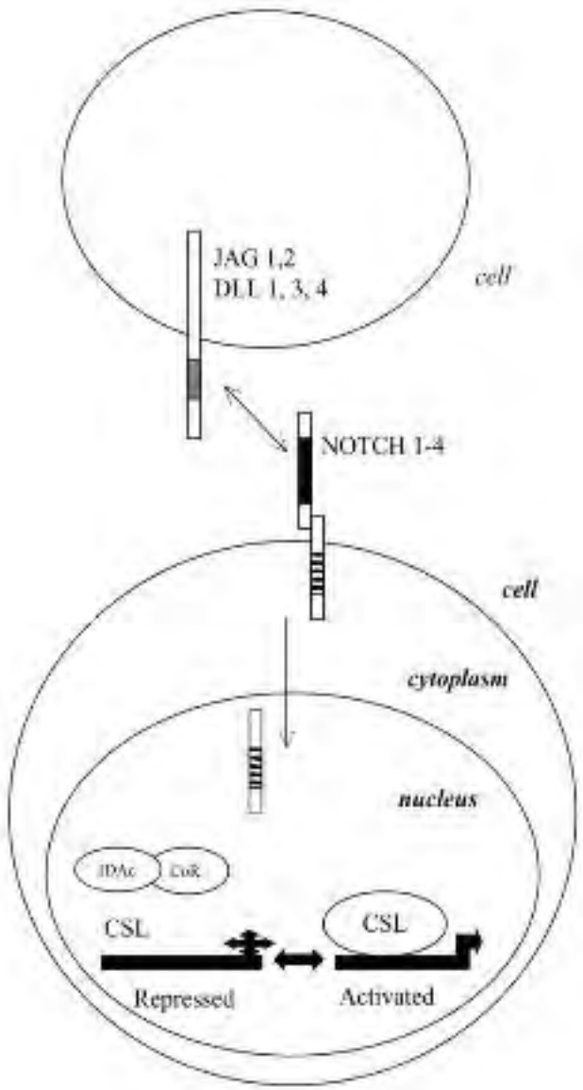


Fig. 3

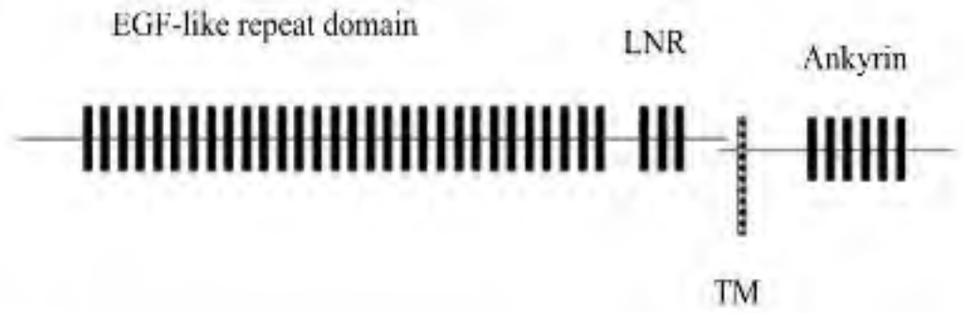
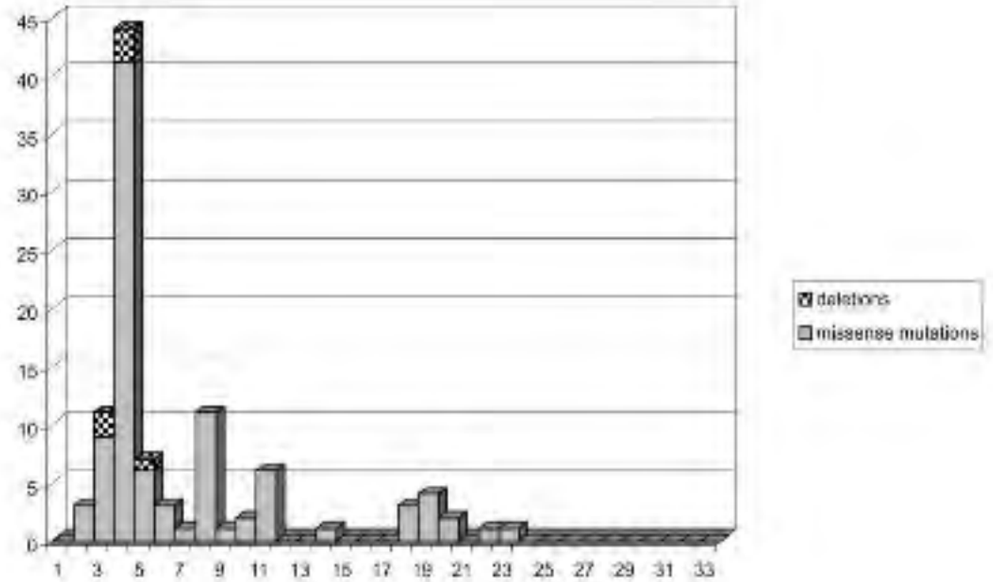


Fig. 4



Amos D. Korczyn

[redacted]

COULD DEMENTIA BE PREVENTED THROUGH MODIFICATION OF VASCULAR RISK FACTORS?

The number of dementia victims keeps increasing at a fast rate, reaching pandemic proportions. Although most research is done in developed countries, underdeveloped communities suffer to the same extent (Ferri, 2005 #601). The victims are not just the patients; the whole family is affected, and the economic impact on society is huge, and will only become larger. A handful of drugs have been developed and are approved for this condition, but unfortunately they have only a small effect, and none can offer a cure. Better solutions will surely be discovered, but are likely to be expensive and not available to everyone, as evidenced from the sad story of HIV therapy. We must attempt to prevent the epidemic, and fortunately several important leads have been identified which justify optimism. In this paper, I attempt to discuss the recently identified risk factors for dementia, and suggest how preventative measures can delay the onset of dementia.

One of the difficulties in drug development is that the pathogenesis of dementia is in most cases poorly understood.

Dementia is not a disease but rather a syndrome that encompasses dozens of clinical entities caused by neurodegeneration, trauma, strokes or infections. The two most common forms of dementia are Alzheimer's disease (AD) and vascular dementia (VaD). Conceptually, AD and VaD are two completely different disorders: The first is a result of a primary neurodegenerative process, the other evolves from damage to the brain through ischemic strokes or hemorrhages. However, the distinction between the two entities is blurred.

The phenomenology of AD and of VaD are largely overlapping and the decision to make one diagnosis rather than the other relies not only on clinical features but also on brain imaging. While imaging criteria for VaD are available, AD diagnosis does not yet have confirmed imaging criteria. Nevertheless, since both brain ischemia and AD are common in old age, they frequently co-occur, making the clinical distinction between AD and VaD, frequently difficult and in my mind unimportant. This is particularly so since there are data to suggest that brain ischemia can enhance the pathologic processes of AD, and vice versa the AD pathology itself induces vascular changes (Korczyn 2002 # 492; De la Torre_____). While in younger demented patients a single mechanism operates, in older people it will be unusual not to find a combination of Alzheimer and vascular pathology (Bennett, 2006 #894)(Korczyn, 2002 #492)(Korczyn, 2002 #321). Forcing the clinician to choose one and abandon another diagnosis is artificial and counter-productive.

Prevention of dementia is theoretically possible if the risk factors are identified and successfully tackled. While early intervention is desirable, it should be recalled that by the time a person develops the first clinical manifestation of AD, brain pathology is already widespread (Bennett, 2006 #894). According to accepted estimates, the preclinical stage of AD may be as long as 10 years. Most of the prospective studies that were done, or are being performed at present, in attempt to reduce the incidence of dementia thus actually refer to secondary prevention, i.e. assess the progression of symptoms rather than of the first appearance of the neuropathological changes, even if this is not usually acknowledged.

The overlap between AD and VaD probably means that there will never be a single mechanism by which this terrible disease can be prevented. However, attention to risk factors is likely to reduce the incidence of dementia. Many risk factors for dementia have been identified, most of which are common, and are responsible for both AD and VaD, as well as to atherosclerosis (Honig, 2005 #869). These include age, hypertension, diabetes mellitus, dyslipidemia, hyperhomocysteinemia, head trauma, smoking, coronary artery disease and low level of eduction and occupational attainment (Ott, 1998 #638)(Seshadri, 2002 #606)(Gustafson, 2003 #895).

Epidemiologic studies cannot always differentiate between risk factors and risk indicators. We know that hypertension is a risk factor for brain damage, including dementia. On the other hand, coronary artery disease is not likely to directly affect the brain. The fact that it is identified in epidemiologic studies may indicate that changes similar to those that occur in the coronary arteries also affect the brain. This distinction is important, because treatment of hypertension can be expected to lower the incidence of dementia, whereas coronary angioplasty not.

In fact, only meager data exists to support the idea that treatment of hypertension is efficacious in reducing the incidence of dementia. One example is the SystEur study, in which elderly subjects with systolic hypertension were treated with either nitrendipine or placebo over only two years. The treatment was efficacious in reducing endpoint events, including the occurrence of dementia. Interestingly, the reduction included cases diagnosed clinically as having AD as well as VaD (Forette, 1998 #888). Retrospective analysis also supports that treatment with statins reduces the occurrence of dementia in patients with hypercholesterolemia (Wolozin, 2000 #893)(Dufouil, 2005 #890).

Supporting evidence on the protective effect of antihypertensive or cholesterol-lowering drugs against dementia is difficult to accumulate. It is unethical to perform placebo-controlled studies on the treatment of these disorders. Syst-Eur was possible since at the time there was no consensus whether systolic hypertension per se should be treated in the elderly, but evidence that treatment of more severe hypertension can reduce the incidence of dementia does not exist. However, this may be a moot point: There is sufficient evidence that hypertension should be treated for other indications, particularly in younger people. Data supporting the protective effect of statins are also accumulating slowly (Dufouil___).

Obesity is another risk factor, which has also been associated with the occurrence of dementia (Gustafson, 2003 #895). Of course, no randomized studies can ever be performed to establish whether prevention of obesity can reduce the icidence of dementia. Nevertheless, nobody is likely to contest the idea that overweight is bad for health in general, and attempts to reduce obesity are promoted by physicians even without referring to the cognitive aspects.

It is with this view that we have to approach the other risk factors mentioned above. Most of these risk factors predispose to the occurrence of dementia several decades later. Low level of education and head trauma are examples of such delayed effects, but this is also true for hypertension, hyperlipidemia and more.
Some of the modifiable risk factors that have been suggested in the literature, like smoking or obesity, may act through a vascular link. Others, like intellectual activities, may have different mechanisms. It is however important to realize that an interaction exists between these factors. For example, highly educated people are more likely to follow a healthy lifestyle, eat a healthy diet, not smoke, be involved in stimulating intellectual activities, promote their physical health through more strict attention to hypertension and hypercholesterolemia, etc. This may make it much more difficult to separate individual components potentially contributing to or slowing intellectual decline in old age.
Not all the factors mentioned here are equally important (and data are missing on several), and some may be redundant to others. Nevertheless, it is more than reasonable to promote physical health, particularly by alluding to the risk factors mentioned above, in order to prevent dementia. Since the prevalence of dementia doubles every 5 years after age 65, delaying the onset of dementia by ten years could reduce age-specific prevalence, particularly in people who are still in critical productive years. This is probably achievable.

References

Bennett DA, Schneider JA, Arvanitakis Z, et al (2006) Neuropathology of older persons without cognitive impairment from two community-based studies. Neurology 66:1837-1844.

Dufouil C, Richard F, Fievet N, Dartigues JF, Ritchie K, Tzourio C, Amouyel P, Alperovitch A (2005) APOE genotype, cholesterol level, lipid-lowering treatment, and dementia: The Three-City Study. Neurology 64:1531-1538.

Ferri CP, Prince M, Brayne C, et al (2005) Global prevalence of dementia: a Delphi consensus study. Lancet 366:2112-2117.

Forette F, Seux M-L, Staessen JA, Thijs L, Birkenhager WH, Babarskiene M-R, Babeanu S, Bossini A, Gil-Extremera B, Girerd X, Laks T, Lilov E, Moisseyev V, Tuomilehto J, Vanhanen H, Webster J, Yodfat Y, Fagard R, on behalf of the Syst-Eur Investigators (1998) Prevention of dementia in randomized double-blind placebo-controlled systolic hypertension in Europe (Syst-Eur) trial. Lancet 352:1347-1351.

Gustafson D, Rothenberg E, Blenow K, Steen B, Skoog I (2003) An 18-year follow-up of overweight and risk of Alzheimer disese. Arch Int Med 163:1524-1528.

Hayden KM, Zandi PP, Lyketsos CG, Khachaturian AS, Bastian LA, Charoonruk G, Tschanz JT, Norton MC, Pieper CF, Munger RAG, Breitner JCS, Welsh-Bohmer KA (2006). Vascular risk factors for incident Alzheimer disease and vascular dementia: The Cache County Study. Alzheimer Dis Assoc Disord 20:93-100.

Honig LS, Kukull W, Mayeux R (2005) Atherosclerosis and AD: Analysis of data from the US National Alzheimer's Coordinating Center. Neurology 64: 494-500.

Korczyn AD (2002a) Mixed dementia the most common cause of dementia. Ann. N.Y. Acad. Sci 977:129-134.

Korczyn AD (2002b) The complex nosological concept of vascular dementia. J Neurol Sci 204: 3-6.

Neuropathology group of the medical research council cognitive function and ageing study (MRC CFAS) (2001) Pathological correlates of late-onset dementia in a multicentre, community-based population in England and Wales. Lancet 357:169-175.

Ott A, Slooter AJC, Hofman A, van Karskamp F, Witteman JCM, Van Broeckhoven C, van Duijn CM, Breteler MMB (1998) Smoking and risk of dementia and Alzheimer's disease in a population-based cohort sdtudy: the Rotterdam Study. Lancet 351:1840-1843.

Seshadri S, Beiser A, Selhub J, Jacques PF, Rosenberg IH, D'Agostino RB, Wilson PWF, Wolf PA (2002) Plasma homocysteine as a risk factor for dementia and Alzheimer's disease. N Engl J Med 346:476-483.

Wolozin B, Kellman W, Ruosseau P, Celesia GG, Siegel G (2000) Decreased prevalence of Alzheimer disease associated with 3-hydroxy-3-methyglutaryl coenzyme A reductase inhibitors. Arch Neurol 57:1439-1443.

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PHARMACOLOGICAL TREATMENT OF ALZHEIMER'S DISEASE

A century has passed since Dr. Alois Alzheimer diagnosed his first patient with a terrible disease that continues today to raise serious challenges in several fields of medicine.

Review of therapeutically strategies
Treatment strategies are classified according to their patterns of action as well as their efficacy:
Symptomatic - modification of the brain function without change of the disease progression;
Disease modifying - intervention in the pathogenetic event;
Preventive - affecting the disease occurrence.

Symptomatic treatment

Current operative treatments are mainly symptomatic based on deficits transmitter substitutions, (e.g. acetylcholine). Efficacy of acetylcholinesterase inhibitors (AchEI) has been evaluated across three key symptom domains of AD cognition, behavior and activities of daily living (ADL) and short symptomatic improvements up to one year have been reported.

Until now, there are five drugs approved by the Food and Drug Administration (FDA) for the treatment of clinically probable AD, but only four of them are used with regularity.
Acetylcholine is involved in many aspects of cognition including memory and attention.

The first compound approved was tacrine (Cognex) and it led the way for treatment of AD (q.i.d. dosing and did have liver toxicity).

Donepezil (Aricept) was the next acetylcholinesterase inhibitor approved by the FDA and became available in the mid 1990s. It is a drug that can be administered with a single dose on a daily basis and does not require any laboratory monitoring.

The drug has been approved for mild to moderate AD and the length of the response has been documented up to 52 weeks. It is uncertain if the actual degree of benefit persists longer than this, but the initial studies of 24 weeks have been extended to 52 weeks.

Studies have indicated that when Donepezil is discontinued, performance of the subject returns to the same as in the untreated state.

Another acetylcholinesterase inhibitor and butyrylcholinesterase inhibitor Rivastigmine (Exelon) has been approved by the FDA as well.
The effect of rivastigmine on the ADAS-Cog and the CIBIC Plus is approximate the same as donepezil.
The fourth cholinesterase inhibitor, Galantamine (Reminyl, Razadyne) is a reversible inhibitor of cholinesterase but has some nicotinic receptor activity. The effect size of galantamine on the ADAS-Cog the CIBIC Plus is similar to donepezil and rivastigmine.Memantine (Namenda), has recently been approved for the treatment of moderate and severe AD. This drug can be used in addition the cholinesterase inhibitors but have no effect on the underlying disease process.

They generally appear to be equally efficacious with regard to their effects on cognition and behavior and they have a similar side-effect profile. The cost of these medications on a daily basis is approximately equivalent. While the effects are modest, they are the recommended mode of treatment for patients with mild to moderate AD.

Nevertheless, the quality of life of the patients and that impact on their caregivers appears to be significant.

There have been few studies in which the drugs have been compared to each other so there is little to recommend one over the other.

Disease modifying treatment

Vitamin E - Considerable research has indicated that there is oxidative damage present in the brains of AD patients. Consequently, the use of antioxidants in the treatment of AD has gained popularity. There are epidemiological data suggesting that antioxidants may be associated with a lower incidence of AD.

One large clinical trial has been conducted in moderate AD patients, and this study showed that vitamin E and selegiline were effective at delaying the progression of moderate AD to a more severe state. This single positive study for vitamin E needs to be interpreted in the context of a recent meta-analysis of vitamin E, indicating that at daily doses of 400 IU or more, there was an increased risk of death mostly from cardiovascular causes.

Amyloid treatments

There are several ways of interfering with the β-amyloid production and clearance:
Blocking β and γ-secretases activity
Immunization therapy
Neuroprotective therapy with neurotrophic factors against APP and tau hyperphosphorylation

β and γ-secretases inhibitors

Several γ-secretase inhibitors have been identified and maybe used in clinical studies. However, toxic consequences occur because γ-secretase is essential for notch signal transduction, for the processing of epidermal growth factors (ErbB4) and many other substrates.
Eli Lilly and CO. developed a functional gamma-secretase inhibitor LY450139. Results of a multicentric double blind placebo controlled 12 week study, with this molecule (30 mg, single dose /day) give as add-on therapy to the patient's standard cholinesterase inhibitor, showed for a limited group of patients measurable changes of amyloid-beta in the plasma and CSF but no changes in cognition as measured by ADAS-Cog.

Immunization therapy

In 1999, Schenk and colleagues immunized against β-amyloid, a transgenic mice who overexpressed a human mutant form of APP, showing many of the pathological features of AD. They demonstrated significantly reduced β-amyloid plaque formation later in life, if immunization occurred at birth.
Mice immunized in mid-life showed a reduction in further progression of the disease with a suggestion of regression of the underlying pathology.
A human randomized clinical trial was initiated in an international multicenter Phase II study of active immunotherapy with a vaccine against β-amyloid-42 (AN1792) plus adjuvant QS-21 in 2001. The study was stopped in early 2002 after a subacute meningoencephalitis was found in approximately 5% of the subjects immunized. The subjects were followed clinically and there was a suggestion that a subset of them who developed sufficient antibody levels may have had a, slowing of the progression of the disease.

Neuroprotective therapy with neurotrophic factors against APP and tau hyperphosphorylation

Neurotrophic factors are playing a key role in therapy. Unfortunately, due to a high molecular weight they can not penetrate the Blood Brain Barrier.
CEREBROLYSIN is a mixture of active fragments of different neurotrophic factors (low molecular weight peptides). Recent clinical trials have shown that Cerebrolysin alleviates some symptoms in patients with mild to moderate AD. (Ruether et al 2001 and 2002; Panisset et al 2002; Bae et al 2000).
CEREBROLYSIN neuroprotective effects in APP tg models are in part related to the ability of this compound to reduce amyloid production.
Cerebrolysin reduces amyloid production by decreasing APP-p, but Has no effects on APP processing or degrading enzymes. Reduced APP-p results in decreased APP transport to the synapse and decreased APP available for processing to Ab.
Cerebrolysin reduces APP-p by decreasing CDK5 and GSK3b activity but does not affect SAPK1. The mechanisms through which Cerebrolysin decreases CDK5 and GSK3b activity are under investigation.
Dr. Tuszynski and colleagues, from La Jolla, California and Chicago, Illinois; and Irvine, California, presented the results of the first patients to receive nerve growth factor (NGF) via instillation through a burr hole, with the implantation of NGF as an ex vivo gene therapy directly into the patients' brains in the nucleus basalis.
Investigators used primary fibroblasts from early-stage AD patients and genetically modified these cells to produce and secrete NGF in an attempt to ameliorate cholinergic cell loss
Positron emission tomographic (PET) scans showed increased glucose metabolism as compared with the baseline, indicating a cholinergic effect of NGF. Cognitive testing at 6 and 18 months showed less of a decline than expected but no cognitive improvement

Nonsteroidal anti-inflammatory drugs

Epidemiological studies indicate that the use of nonsteroidal anti-inflammatory drugs (NSAIDs) may protect against developing AD.
Several epidemiological studies appear to imply that NSAIDs may be of benefit in potentially postponing the development of AD none of the randomized clinical trials has been able to corroborate these findings. In addition, concern has been raised about the safety of COX-2 inhibitors and perhaps other NSAIDs as well. NSAIDs beeing currently recommended neither for the treatment nor the prophylaxis of developing AD.

Estrogen therapy

There has been some epidemiological evidence indicating that post-menopausal women who take estrogen replacement may be protected from developing AD.
A large randomized, double-blind, placebo-controlled trial in mild to moderate AD failed to demonstrate the benefit of estrogen replacement therapy over the course of 12 months.

Cholesterol lowering therapy

Two retrospective clinical studies indicate that there is a decreased prevalence of Alzheimer's disease associated with the use of statins to treat hypercholesterolemia.

Animal studies have revealed that association of amyloid production and cholesterol
depletion seems to inhibit the amyloidogenic (β -and γ-secretase) pathway, while stimulating the non-amyloidogenic (α-secretase) pathway.
Some clinical studies suggested that treatment of patients with LLAs may have a beneficial effect on slowing cognitive decline.
Evidence Report - Pharmacological Treatment of Dementia (U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES)

Delay of Onset of Dementia

The concept of "delay onset" was operationalized to imply conversion from a state of cognitive impairment (classified as MCI, CLoND or CIND), to a true dementia state.

The lack of studies eligible for evaluation in this systematic review points to a gap in the literature for pharmacological interventions (attempting to demonstrate a delay in disease onset) in MCI-type populations.

Delay of Progression of Dementia

Studies evaluating Cerebrolysin, selegiline plus vitamin E, and donepezil have shown statistically significant effects in delaying disease progress in mild to moderate and moderately severe disease in patients with AD.
This delay in progress was expressed in terms of delay in days to primary event or statistical differences between placebo at a specified time interval.
A total of 26 studies compared efficacy of the two or more pharmacological agents relative to each other.

References:

Doody RS, Stevens JC, Beck C, et al. Practice parameter: Management of dementia (an evidence-based review): Report of the Quality Standards Subcommittee of the American Academy of Neurology.Neurology 2001;56:1154-1166

Tariot PN, Solomon PR, Morris JC, et al. A 5-month, randomized, placebo-controlled trial of galantamine in AD. Neurology 2000;54:2269-2276

Sano M, Ernesto C, Thomas R, et al. A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease: The Alzheimer's Disease Cooperative Study. N Engl J Med 1997;336:1216-1222

Miller ER 3rd, Pastor-Barriuso R, Dalai D, Riemersma RA, Appel LJ, Guallar E. Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality. Ann Intern Med 2005;142:37-46

Siemers E, Quinn J, Kaye J, et al. Effect of LY450139, a functional gamma-secretase inhibitor, on plasma and cerebrospinal fluid concentrations A-beta and cognitive functioning in patients with mild to moderate Alzheimer's disease. Neurology. 2004;62(suppl5):A174. Abstract S17.001.

Orgogozo JM, Gilman S, Dartigues JF, et al. Subacute meningoencephalitis in a subset of patients with AD after Abeta42 immunization. Neurology 2003;61:46-54

Gilman S, Roller M, Black RS, et al. Clinical effects of Abeta immunization (AN1792) in patients with AD in an interrupted trial. Neurology 2005;64:1553-1562

Masliah E, Hansen L, Adame A, et al. Abeta vaccinationeffects on plaque pathology in the absence of encephalitisin Alzheimer disease. Neurology 2005;64:129-131

Fox NC, Black RS, Gilman S, et al. Effects of Abeta immunization (AN1792) on MRI measures of cerebral volume in Alzheimer disease. Neurology 2005;64:1563-1572

Lise A. Labiche and James C. Grotta NeuroRx®: The Journal of the American Society for Experimental NeuroTherapeutics, Clinical Trials for Cytoprotection, Vol. 1, 46-70, January 2004 © The American Society for Experimental NeuroTherapeutics, Inc.

Tuszynsik M, Thal L, Pay M, et al. A phase I trial of nerve growth factor ex vivo gene therapy for Alzheimer's disease. Neurology. 2004;62(suppl5):A174-175. Abstract S17.002.

Topol EJ. Failing the Public HealthRofecoxib, Merck and the FDA. N Engl J Med 2004;351:1707-1709

Weggen S, Ericksen JL, Sagi SA, et al. Evidence thatnonsteroidal anti-inflammatory drugs decrease amyloidbeta42 production by direct modulation of gamma-secretase activity. J Biol Chem 2003;278:31831-31837

Henderson VW, Paganini-Hill A, Miller BL, et al. Estrogen for Alzheimer's disease in women: Randomized, double-blind, placebo-controlled trial. Neurology 2000;54:295-301

Wolozin B, Kellman W, Ruosseau P, Celesia GG, Siegel G. Decreased prevalence of Alzheimer disease associated with 3-hydroxy-3-methy-glutaryl coenzyme A reductase inhibitors. Arch Neurol 2000; 57:1439-1443.

Jick H, Zornberg GL, Jick SS, Seshadri S, Drachman DA. Statins and the risk of dementia. Lancet 2000; 356:1627-1631

Simons M, Schwarzler F, Lutjohann D,von Bergmann K, Beyreuther K,Dichgans J, Wormstall H, Hartmann T, Schulz JB. Treatment with simvastatin in normocholesterolemic patients with Alzheimer's disease: a 26-week randomized, placebo-controlled double-blind trial. Ann Neurol 2002; 52:346-350.

Thomas A, Iacono D, Bonanni L, et al. Donepezil, rivastigmine, and vitamin E in Alzheimer disease: a combined P300 event-related potentials/neuropsychologic evaluation over 6 months. Clin Neuropharmacol 2001 Jan; 24(1):31-42.

Gutzmann H, Kuhl KP, Hadler D, et al. Safety and efficacy of idebenone versus tacrine in patients with Alzheimer's disease: results of a randomized, double-blind, parallel-group multicenter study. Pharmacopsychiatry 2002 Jan; 35(1):12-8.

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GENES INVOLVED IN DEMENTIA

Alzheimer's disease

Alzheimer's disease (AD) is the most frequent cause of age-related progressive dementia, which constantly leads to profound alteration of cognitive functions and premature death. A certain AD diagnosis has still to be confirmed post-mortem and relies on the presence of senile plaques (SP), neurofibrillary tangles (NFT) and widespread neuronal degeneration, the pathological hallmarks of the disease. A reduction in weight with 20 % or more is characteristic for AD brains and is due to atrophy, which is the macroscopic proof of cell loss. Both cell death and loss of synapses account for the clinical manifestations of the disease (Selkoe, 2002). Brain atrophy affects the temporal, parietal and frontal lobes, in this order. SP consist of extracellular core accumulations of beta amyloid peptide (Aβ), surrounded by morphologically altered nerve terminals, especially dendrites, with abnormal lysosomes and mitochondria. Aβ results from the β-amyloid precursor protein (APP), which is substrate of a complex proteolytic processing by proteases, called secretases. NFT are found within neurons and are formed by paired helical filaments (PHFs) of hyperphosphorylated microtubule-associated protein tau.

Based on genetic and epidemiological data, AD is classified as either sporadic or familial (FAD). Highly penetrant mutations in genes encoding presenilin 1 (PS1), presenilin 2 (PS2) or APP are associated with early onset FAD but account for only approximately 1% of all AD cases (St. George-Hyslop, 2000). In addition, carriers of apolipoprotein E (apoE) allele ε4 have a higher risk to develop AD and a lower age of onset of the disease, and brains of ε4 AD cases have more severe plaque and tangle pathology (Cedazo-Minguez and Cowburn, 2001). Other unidentifiedsusceptibility genes have been suggested for AD, for instance localized to chromosomes 10 (Bertram et al., 2000) and 12 (Pericak-Vance et al., 1997) but they have not been cloned yet and the link to AD is not clearly established.

To date the cause and progression of AD are not fully understood. Two major pathogenic scenarios emerged in the last decade to explain the neuronal dysfunction and loss: the amyloid cascade hypothesis (Hardy and Higgins, 1992) and the cytoskeleton degeneration hypothesis (Braak and Braak, 1991).

AMYLOID PRECURSOR PROTEIN (APP) AND Aβ GENERATION

APP is an evolutionary conserved type I membrane protein with a wide tissue distribution, including neurons. APP has a short C-terminal domain located to the cytosol and a long N-terminal domain located to lumen or is extracellular. Different APP mRNAS arise from the splicing of a gene located on chromosome 21 (APP-695, APP-751, APP-770), and other proteins with similar structure with APP exist and are called APLPs (Suh and Checler, 2002). APP physiological functions are not fully elucidated yet, but roles in axonal transport, synaptic plasticity, neuroprotection, cell growth and cell adhesion, were suggested (De Strooper and Annaert, 2000). APP normally undergoes proteolysis by α-secretase within the Aβ domain to yield a secreted form (α-APPs), and further processing of the remaining CTF by γ-secretase result in a small peptide (p3) and an APP intracellular domain (AICD). An alternative processing pathway involving β- and γ-secretases generate β-APPs, Aβ peptide and AICD. Two members of a disintegrin and metalloprotease family (ADAM), ADAM-10 and ADAM-17 (TACE) are candidates for α-secretases, a transmembrane aspartyl-protease, BACE (Asp-2) was identified as β-secretase and a high molecular weight multiprotein complex consisting of PSs, Nicastrin, Aph-1 and Pen-2 executes the γ-secretase activity (Suh and Checler, 2002, Edbauer et al., 2003). Presenilins are essential for the γ-secretase activity and production of A. Cells from PS1/PS2 double-knockout mice do not produce any A, by complete abolishment of the -secretase activity (Herreman et al., 2000, Zhang et al., 2000), which proves that presenilins are needed for APP processing and A generation. However, another group reported that in mice fibroblasts deficient in both PS1 and PS2, Aβ production still takes place (Armogida et al., 2001). Mutations in genes encoding APP or PSs result in an enhanced production of longer, more fibrillogenic forms of Aβ (Suzuki et al., 1994).

Different functions have been attributed to each proteolytic product derived from APP. The soluble (secreted) forms of APP were proposed to be neuroprotective and to play a role in learning and memory (Turner et al., 2003). The small peptide p3 has no known function so far. The AICD activates gene expression by coupling with the nuclear adaptor protein Fe65 (Cao and Sudhoff, 2001) and this transcriptional activity is downregulated by activation of the NF-kappaB pathway (Zhao and Lee, 2003). Some reports suggest a neurotoxic activity also for C-terminal APP species (Suh and Checler, 2002). Finally, a large body of evidence supports that Aβ peptide is toxic. A has been shown to be toxic to cells in culture both when applied extracellulary or after microinjection (Zhang et al., 2002). It seems that mainly the intracellular form and not the secreted one is responsible for the neurotoxicity (Echeverria and Cuello, 2002). The oxidative effects of A may be mediated through interaction with redox-active metals since metal chelation treatment of A significantly attenuates toxicity. It has also been argued that A is an anti-oxidant and produced to protect cells from oxidative challenge (Rottkamp et al, 2002). Other mechanisms involved in Aβ neurotoxicity are alteration of Ca^{2+} homeostasis (Mattson et al., 1992), enhancement of glutamate-mediated toxicity (Harkany et al., 2000), microglial activation with cytokines release (Hu et al., 1998), activation of MAPK with subsequent tau hyperphosphorylation (Rapoport and Ferreira, 2000). The amyloid cascade hypothesis bases on all these data and states that tau hyperphosphorylation is induced by altered APP processing and Aβ generation.

TAU PROTEIN AND NEUROFIBRILLARY TANGLES

Tau is a microtubule-associated phosphoprotein which is expressed in both central and peripheral nervous system, mainly in neurons. Tau binds to tubulin, promoting microtubules assembly and stability. The balance of tau phosphorylation / dephosphorylation modulates the stability of the cytoskeleton and the axonal morphology. In AD brains, tau becomes hyperphosphorylated in its C-terminal region, which contains the microtubule-binding domain. The hyperphosphorylated tau forms paired helical filaments (PHFs) which in turn form the neurofibrillary tangles. More than 20 phosphorylation sites have been identified for tau (Hanger et al., 1998). Many different kinases have been shown to phosphorylate tau, including cycline dependent kinases 2 and 5, mitogen-activated protein kinase, Ca^{2+}-calmodulin-dependent protein kinase II, PKA, PKC, but the most important tau kinase in the brain seems to be glycogen synthase kinase-3 β (GSK-3β, Lovestone and Reynolds, 1997). Tau is dephosphorylated by both protein phosphatase 2A (PP2A) and 2B (PP2B), but PP2A is by far predominant (Billingsley and Kincaid, 1997).

In AD, the balance between the activity of tau kinases and phosphatases is altered and the hyperphosphorylated tau leads to impaired fat axonal transport and finally to neurodegeneration. The neurofibrillary tangle pathology matches both the areas of neuronal loss and the degree of cognitive deterioration. However, evidence presented by a recent study has suggested that tangle formation could be secondary to altered APP processing (Oddo et al., 2003).

PRESENILINS (PSs)

In 1995, genes encoding PS1 and PS2 were identified on chromosome 14 and chromosome 1, respectively, and mutations of these genes were correlated with a large number of FAD cases. To date, more than 150 pathological mutations of PS1 and only a few of PS2 were detected in FAD cases. All these are missense mutations that generate single amino acid substitutions in the protein primary structure, with the exception of PS1 exon 9 deletion splice mutation (Popescu and Ankarcrona, 2000).

PS1 and PS2 are multipass membrane proteins sharing 60% amino-acid sequence homology and are predicted to contain 6 to 8 transmembrane (TM) domains (Doan et al., 1996). Between TM domains 6 and 7 they contain a large hydrophilic loop, on the cytosolic side of the membrane. The cytoplasmic loop includes the sites where different proteolytic cleavages of PSs occur. A physiological endoproteolytic cleavage by an elusive protease known as "presenilinase" occurs within the exon 9 encoded region of PSs, between residues Thr_{291} and Ala_{299} (Podlisny et al., 1997). From this cleavage result a ~30 kDa N-terminal fragment and a ~20 kDa C-terminal fragment, which accumulate in cells with a 1:1 stoichiometry and represents the main PSs species in human tissues (Podlisny et al., 1997). The NTF and CTF form a functional heterodimer, which is a part of a high molecular weight complex consisting of several molecular partners (Nicastrin, Aph-1 and Pen-2) which executes the -secretase cleavage of APP described above (Edbauer et al., 2003).

PSs are ubiquitous proteins, being identified in most human organs, e.g. brain, lung, heart, liver and muscle (Okochi et al., 1998). Within the brain, PSs are present in variable amounts in all regions, mainly in the neocortex, hippocampal pyramidal neurons and magnocellular basal forebrain neurons (Lee et al., 1996), areas primarily affected by AD. Within the cells, PSs are mainly located to the endoplasmic reticulum (ER) and Golgi apparatus (Kovacs et al., 1996), but also to the nuclear envelope (Li et al., 1997), to the plasma membrane (Dewji and Singer, 1997) and to the mitochondrial inner membrane (Ankarcrona and Hultenby, 2002).

A wealth of data shows that the main function of PSs consists in enabling regulated intramembrane proteolysis (RIP) through γ-secretase activity.

Presenilins are important during development since the cleavage of NOTCH and the subsequent generation of NICD, a C-terminal fragment of NOTCH involved in gene regulation, is dependent on functional presenilin (Struhl and Greenwald, 1999).

Mutated PSs could cause FAD by triggering various pro-apoptotic mechanisms, which would be in agreement with the hypothesis that cell loss in AD is due to apoptosis. Many reports have shown that different PSs FAD mutations sensitize cells to apoptosis triggered by several stimuli. These data suggest that neurons bearing mutant PSs are more prone to undergo apoptosis when exposed to stressful stimuli, which could explain why FAD brains show extensive neurodegeneration at an early age.

APOLIPOPROTEIN E

In contrast to APP and PSs, which are determinant genetic factors, a genetic risk factor for AD is the E4 allele of the apolipoprotein E (ApoE) gene. E4 baring individuals have higher risk for developing AD and have lower age of onset. Moreover, brains of E4 AD cases present more severe plaque and tangle pathology, but inheritance of E4 is not either essential or sufficient on its own to cause AD. The current pathogenic scenarios claim that ApoE binds to Aβ and influences deposition formation and that E4 allele associate with a dysfunction in lipid transport which eventually causes alteration of plasticity and synaptic integrity (Cedazo-Minguez and Cowburn, 2001).

Frontotemporal dementia

Frontotemporal dementia (FTD) is the second most frequent type of neurodegenerative dementia. It seems that etiologically FTD is a complex disorder, genetic factors contributing essentially to the disease process (Knibb et al., 2006). A part of approximately 20% of FTD patients are characterized by an autosomal dominant inheritance and associates parkinsonism, being defined as 'FTD and parkinsonism linked to 17q21' (FTDP-17). These patients have mutations in the microtubule associated protein tau (MAPT) gene and the neuropathological examination of their brains reveals intracellular inclusions of tau protein (Froelich-Fabre et al., 2004). Other 33% of FTD patients do not have tauopathy, but ubiquitin inclusions at the neuropathological examination. Mutations in tau gene lead to the abnormal intracellular aggregation of tau protein and a progressive neuronal loss.

Several disorders were identified to be linked to tau pathology (tauopathies, e.g. Alzheimer's disease, corticobasal degeneration, Hallervorden-Spatz disease, multiple system atrophy, progressive supranuclear palsy, subacute sclerosing Panencephalitis, Down syndrome, dementia pugilistica, etc.), and in each of these cases tau pathology was identified in the frontal brain lobes. Some of the tauopathies associate senile plaques as well (Alzheimer's disease, Down's syndrome, dementia pugilistica).

References

Ankarcrona, M. and Hultenby, K., Presenilin-1 is located in rat mitochondria, Biochem Biophys Res Commun 295 (2002) 766-770.

Armogida, M., Petit, A., Vincent, B., Scarzello, S., daCosta, C.A. and Checler, F., Endogenous beta-amyloid production in presenilin-deficient embryonic mouse fibroblasts, Nat Cell Biol 3 (2001) 1030-1033.

Bertram, L., Blacker, D., Mullin, K., Keeney, D., Jones, J., Basu, S., Yhu, S., McInnis, M.G., Go, R.C., Vekrellis., K., Selkoe, D.J., Saunders, A.J. and Tanzi, R.E., Evidence for genetic linkage of Alzheimer's disease to chromosome 10q, Science 290 (2000) 2302-2303.

Billinsgley, M.L. and Kincaid, R.L., Regulated phosphorylation and dephosphorylation of tau protein: effects on microtubule interaction, intracellular trafficking and neurodegeneration, Biochem J 323 (1997) 577-591.

Braak, H. and Braak, E., Neuropathological staging of Alzheimer-related changes, Acta Neuropathol 82 (1991) 239-259.

Cao, X and Sudhoff, T.C., A transcriptively active complex of APP with Fe65 and histone acetyltransferase Tip 60, Science 293 (2001) 115-120.

Cedazo-Minguez, A. and Cowburn, R.F., Apolipoprotein E: a major piece in the Alzheimer's disease puzzle, J Cel Mol Med, 5 (2001) 254-266.

De Strooper, B. and Annaert, W., Proteolytic processing and cell biological functions of the amyloid precursor protein, J Cell Sci 113 (2000) 1857-1870.

Dewji, N.N. and Singer, S.J., Cell surface expression of the Alzheimer disease-related presenilin proteins, Proc Natl Acad Sci USA (1997) 9926-9931.

Doan, A., Thinakaran, G., Borchelt, D.R., Slunt, H.H., Ratovitsky, T., Podlisny, M., Selkoe, D.J., Seeger, M., Gandy, S.E., Price, D.L. and Sisodia, S.S., Protein topology of presenilin 1, Neuron 17 (1996) 1023-1030.

Echeverria, V. and Cuello, A.C., Intracellular A-beta amyloid, a sign for worse things to come? Mol Neurobiol 26 (2002) 299-316.

Edbauer, D., Winkler, E., Regula, J.T., Pesold, B., Steiner, H. and Haass, C., Reconstitution of γ-secretase activity, Nat Cell Biol 5 (2003) 486-488.

Froelich-Fabre, S., Skoglund, L., Ostojic, J., Kilander, L., Lindau, M., Glaser, A., Basun, H., Lannfelt, L., Clinical and molecular aspects of frontotemporal dementia, Neurodegener Dis 1 (2004) 218-24.

Hanger, D.P., Betts, J.C., Loviny, T.L., Blackstock, W.P. and Anderton, B.H., New phosphorylation sites identified in hyperphosphorylated tau (peired helical filament-tau) from Alzheimer's disease brain using nanloelectrospray massspectrometry, J Neurochem 71 (1998) 2465-2476.

Hardy, J.A. and Higgins, G.A., Alzheimer's disease: the amyloid cascade hypothesis, Science 256 (1992) 184-185.

Harkany, T., Abraham, I., Timmerman, W., Laskay, G., Toth, B., Sasvari, M., Konya, C., Sebens, J.B., Korf, J., Nyakas, C., Zarandi, M., Soos, K., Penke, B. And Luiten, P.G. Beta-amyloid neurotoxicity is mediated by a glutamate-triggered excitotoxic cascade in rat nucleus basalis, Eur J Neurosci 12 (2000) 2735-2745.

Herreman, A., Hartmann, D., Annaert, W., Saftig, P., Craessaerts, K., Serneels, L., Umans,L., Schrijvers, V., Checler, F., Vanderstichele, H., Baekelandt, V., Dressel, R., Cupers,

P., Huylebroeck, D., Zwijsen, A., Van Leuven, F. and De Strooper, B., Presenilin 2 deficiency causes a mild pulmonary phenotype and no changes in amyloid precursor protein processing but enhances the embryonic lethal phenotype of presenilin 1 deficiency, Proc Natl Acad Sci USA 96 (1999) 11872-11877.

Hu, J., Akama, K.T., Krafft, G.A., Chromy, B.A. and Van Eldik, L.J., Amyloid-beta peptide activates cultured astrocytes: morphological alterations, cytokine induction and nitric oxide release, Brain Res 785 (1998) 195-206.

Knibb, J.A., Kipps, C.M., Hodges, J.R., Frontotemporal dementia, Curr Opin Neurol. 19 (2006) 565-571.

Kovacs, D.M., Fausett, H.L., Page, K.J., Kim, T.W., Moir, R.D., Merriam, D.E., Hollister, R.D., Hallmark, O.G., Mancini, R., Felsenstein, K.M., Hyman, B.T., Tanzi, R.E. and Wasco, W., Alzheimer-associated presenilins 1 and 2: neuronal expression in brain and localization to intracellular membranes in mammalian cells, Nat Med 2 (1996) 224-229.

Lee, M.K., Slunt, H.H., Martin, L.J., Thinakaran, G., Kim, G., Gandy, S.E., Seeger, M., Koo, E., Price, D.L. and Sisodia, S.S., Expression of presenilin 1 and 2 (PS1 and PS2) in human and murine tissues, J Neurosci 16 (1996) 7513-7525.

Li, J., Xu, M., Zhou, H., Ma, J. and Potter, H., Alzheimer presenilins in the nuclear membrane, interphase kinetochores, and centrosomes suggest a role in chromosome segregation, Cell 90 (1997) 917-927.

Lovestone, S. and Reynolds, C.H., The phosphorylation of tau: a critical stage in neurodevelopment and neurodegenerative processes, Neuroscience 78 (1997) 309-324.

Mattson, M.P., Cheng, B., Davis, D., Bryant, K., Lieberburg, I. and Rydel, R.E., Beta-amyloid peptides destabilize calcium homeostasis and render human cortical neurons vulnerable to excitotoxicity, J Neurosci 12 (1992) 376-389.

Oddo, S., Caccamo, A., Shepherd, J.D., Murphy, M.P., Golde, T.E., Kayed, R., Metherate, R., Mattson, M.P., Akbari, Y. and LaFerla, F.M., Triple transgenic model of Alzheimer's disease with plaques and tangles: intracellular Aβ and synaptic dysfunction, Neuron 39 (2003) 409-421.

Okochi, M., Sahara, N., Kametani, F., Usami, M., Arai, T., Tanaka, K., Ishii, K., Yamamoto, A. and Mori, H., Presenilin 1 cleavage is a universal event in human organs, Neurobiol Aging 19 (1998) S3-S10.

Pericak-Vance, M.A., Bass, M.P., Yamaoka, L.H., Gaskell, P.C., Scott, W.K., Terwedow, H.A., Menold, M.M., Conneally, P.M., Small, G.W., Vance, J.M., Saunders, A.M., Roses, A.D. and Haines, J.L., Complete genomic screen in late-onset familial Alzheimer's disease, JAMA 278 (1997) 1237-1241.

Podlisny, M.B., Citron, M., Amarante, P., Sherrington, R., Xia, W., Zhang, J., Diehl, T., Levesque, G., Fraser, P., Haass, C., Koo, E.H., Seubert, P., St. George-Hyslop, P., Teplow, D.B. and Selkoe, D.J., Presenilin proteins undergo heterogeneous endoproteolysis between Thr291 and Ala299 and occur as stable N- and C-terminal fragments in normal and Alzheimer's brain tissue, Neurobiol Dis 3 (1997) 325-337.

Popescu B.O. and Ankarcrona, M, Neurons bearing presenilins: weapons for defense or suicide? J Cell Mol Med 4 (2000) 249-261.

Rapoport, M. And Ferreira, A., PD98059 prevents neurite degeneration induced by fibrillary beta-amyloid in mature hippocampal neurons. J Neurochem 74 (2000)

Fibrillary beta-amyloid in mature hippocampal neurons. J Neurochem 74 (2000) 125-133.

Rottkamp C.A., Atwood C.S., Joseph J.A., Nunomura A., Perry G., and Smith M.A., The state versus amyloid-: the trial of the most wanted criminal in Alzheimer disease, Peptides 23 (2002) 1333-1341.

Selkoe, D.J., Alzheimer's disease is a synaptic failure, Science 298 (2002) 798-791.

St. George-Hyslop, P.H., Molecular genetics of Alzheimer's disease, Biol Psychiatry 47 (2000) 183-199.

Struhl, G. and Greenwald, I., Presenilin is required for activity and nuclear access of Notch in Drosophila, Nature 398 (1999) 522-525.

Suh, Y.H. and Checler, F., Pharmacol Rev 54 (2002) 469-525.

Suzuki, N., Cheung, T.T., Cai, X.D., Odaka, A., Otvos, L., Eckman, C., Golde, T.E. and Younkin, S.G., An increased percentage of long amyloid beta protein secreted by familial amyloid beta protein precursor (betaAPP717) mutants, Science 264 (1994) 1336-13340.

Turner, P.R., O'Connor, K., Tate, W.P. and Abraham, W.C., Roles of amyloid precursor protein and its fragments in regulating neural activity, plasticity and memory, Prog Neurobiol 70 (2003) 1-32.

Zhang, Z., Nadeau, P., Song, W., Donoviel, D., Yuan, M., Bernstein, A. and Yankner, B.A., Presenilins are required for gamma-secretase cleavage of beta-APP and transmembrane cleavage of Notch-1. Nat Cell Biol 2 (2000) 463-465.

Zhang, Y., McLaughlin, R., Goodyer, C. and LeBlanc A. Selective cytotoxicity of intracellular amyloid peptide 1-42 through p53 and Bax in cultured primary neurons, J Cell Biol 156 (2002) 519-529.

Zhao, Q. and Lee, F.S., The transcriptional activity of the APP intracellular domain-Fe65 complex is inhibited by the activation of the NF-kappaB pathway, Biochemistry 42 (2003) 3627-3634.

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NORMAL BRAIN AGEING - STATES AND SUBSTRATES

Facts about ageing

The neurones, in their post-mitotic state, are one of the most resilient and age-resistant cell type of the human body. Apart from a small number of brain regions that show neuronal replacement through adult neurogenesis (Ming & Song 2005), the very large majority of the billions of neurones present at birth of an individual will remain with her for the remaining seven to nine decades or even longer. However, above every head, the threat of senile dementia hangs like Damocles' sword. By fortune, despite the fact that ageing is one of the major risk factors for various forms of dementia, not everybody develops it. Normal ageing comes with a degree of cognitive decline, recognised and described by natural philosophers thousands of years ago (Verkhratsky et al. 2004). For many individuals, cognitive aging is particularly associated with impairments in remembering recent events and in learning complex associations (Hedden & Gabrieli 2004). Intriguingly, whereas the ability to form memories of new events and associations declines with age, memories of older events are often rigidly retained (Burke & Mackay 1997).

Neuroimaging studies in the last decade have revealed another important aspect of normal brain ageing. While aged brain maintain a certain degree of functional plasticity, its regional recruitment and activation of networks in performing a variety of tasks are significantly different than in the young/adult brain (Reuter-Lorenz 2002).

Despite all these progresses, our understanding of the substrates and mechanisms responsible for the age-dependent impairment of the brain function remains rather superficial, and the science of normal ageing is still in its infancy. A whole Special Issue in Trends in Neurosciences (October 2004, vol. 27) was dedicated to the topic of Normal Brain Ageing. In this minireview, I will present only a brief summary of the major morphological and functional changes induced by ageing, and discuss the principal metabolic mechanisms that underlie these changes. Two further points need to be mentioned at this stage, providing an important backdrop for the foregoing discussion. The first is that normal brain ageing should be seen as a physiological state, probably as equidistant from the "normal" reference state of young adulthood as is infancy, but from a different direction. In many instances "ageing" and "neurodegeneration" are mentioned in the same sentence, as if one represents a normal and expected consequence of the other (e.g., (Terry & Katzman 2001)). As it will be briefly presented here, the wealth of the accumulated evidence suggests that neurodegeneration represents a pathological state superimposed on the physiological state of normal ageing that is characterised by a decreased "homeostatic reserve", which confers increased metabolic vulnerability to the aged neurones (Toescu 2005).

The other observation is that various animals are an important and valid experimental models for the study of ageing, including the age-dependent changes in cognitive function (Gallagher & Rapp 1997), or the more specific changes in hippocampal function (Rosenzweig & Barnes 2003).

States of Ageing

1. Morphological changes. One powerful image of the causes of cognitive dysfunction on the aged brain, an image that permeates not only the popular mind but has a powerful holding grip also on many medical minds, is that of significant and continuous neuronal loss with age. This conviction, that provides a simple link between loss of function and loss of material substrate, has a long history. The first report of disappearance of neurons in old age appears to be that of Hodge (1894), which showed that the ganglia of young honey bees contain 2.9 times more cells than those of old bees. A more consistent series of studies, initiated from the 50s onwards, showed an age-associated neuronal loss variable among different species, ages, regions, and methods. In humans, the number of neurons per unit volume of tissue, or neuron density, appeared to decline markedly - most neocortical areas and certain hippocampal subfields were reported to lose 25 to 50% of their resident neurons with age (e.g., (Brody 1955)). Two seminal review papers, published at 10-year interval (Coleman & Flood 1987; Morrison & Hof 1997), together with the development of much more powerful and accurate stereological counting techniques, have changed this field upside down. Today, there is a general consensus that in most regions of the brain there is no significant neuronal loss with age, in dramatic and powerful contrast with the situation in various neurodegenerative diseases, which are characterised by profound regional neuronal loss (Hof & Morrison 2004; Morrison & Hof 1997). In fact, a 'contamination', in the earlier studies, of the experimental samples with specimens from individuals with early subclinical stages of neurodegenerative diseases might have biased their conclusions.

2. Synaptic changes, morphological and functional. Thus, if neuronal loss cannot explain the mild cognitive decline, what could be the morphological substrate? And the answer lies at the level of the synapses. At a morphological level, in the absence of neuronal degeneration, irregularities in dendritic arborisation and in dendritic spine length or volume, distribution or density, could all have detrimental effects on function. Indeed, analysis of basal dendritic branching patterns of pyramidal cells in human prefrontal cortex revealed a decrease in total dendritic length, total number of dendritic segments and terminal dendritic length with age (de Brabander et al. 1998), with an even more accentuated decrease in the spine density (Jacobs et al. 2001).

Age affects the synaptic compartment not only at the morphological level, but also at a functional level. One of the best-known mechanisms proposed to mediate the processes of learning and memory is that of synaptic plasticity, through which, in a

specific and activity-dependent manner, the efficiency of transmission of information at a particular synapse can be up-regulated (long-term potentiation, LTP) or down-regulated (long-term depression, LTD) (Malenka & Bear 2004). Ageing affects both these processes. In the aged slices, the activation threshold required to induce synaptic LTP is increased only strong stimulations induces LTP in the aged brains, whereas a low amplitude stimulation, sufficient to trigger LTP in young animals, is ineffective in aged animals (Foster & Kumar 2002; Rosenzweig & Barnes 2003). In addition, aged rats are more susceptible than the younger animals to activation of LTD and depotentiation, as a result of a significant reduction in the LTD threshold (Foster & Kumar 2002; Rosenzweig & Barnes 2003). Both these changes can be explained by a modification in the activity of a plasma membrane, Ca^{2+}-dependent K^+ channel that mediates the recovery of the resting membrane potential following an action potential (ie, afterhyperpolarization) (Disterhoft & Oh 2006). The fact that this channel is activated by increases in Ca^{2+}_i provides an important link with the metabolic substrates of neuronal ageing, briefly discussed in the next section.

3. Neuronal network dysfunction. We have recently demonstrated how subtle changes in synaptic activity and neuronal communication can result in disruptions of whole neuronal networks in a study that looked at the effect of ageing on brain oscillatory activity (Vreugdenhil & Toescu 2005). Encoding and retrieval of episodic memory appears to be associated with synchronous neuronal activity in the 30-80 Hz frequency band (γ activity). These oscillations can also provide the means of a synchronization clock, at a millisecond level, necessary for the induction of LTP by a variety of excitatory inputs. When using a model of kainate (KA)- or cholinergic (CCh)-induced γ oscillations in brain slices, we observed that in the aged animals, there was a dramatic decrease (85%) in the power of these oscillations, while the waveform, frequency spectrum and coherence of the oscillations were not affected by age. The theoretical model that explains the generation of such oscillations is quite complex, but our recent unpublished observations indicate that changes in mitochondrial status and enhanced Ca^{2+} signalling are responsible for the reduction in the power of the γ oscillations in the hippocampi of the aged rodents.

Substrates of Ageing

1. Metabolic Theories of Ageing. The preceding sections stressed the important fact that the age-associated changes in brain function and cognitive performance are not due to overt neuronal loss, but to subtle changes in synaptic distribution and synaptic activity. Thus, any attempt to understand the intracellular substrates explaining neuronal ageing should not look for mechanisms that kill the neurones, as is the case in the majority of neurodegenerative diseases, but to modifications that impair only to a certain degree the neuronal performance. For the last four decades, one of the most important theories that tries to explain ageing from a cellular perspective, has been the "free radicals theory of ageing" (FRATA), that proposed that the stochastic accumulation of oxidative-stress induced damage, particularly in post-mitotic cells such as the neurones, explains the metabolic impairment of aged tissues (Harman 1956). In the 80s, two other theories, the "mitochondrial theory of ageing" (Miquel et al. 1980) (MITA) and the "Ca^{2+} theory of ageing" (Khachaturian 1984) (CATA), expanded Harman's theory by providing more specific mechanisms of continuous generation of free radicals and pathways for inducing the damage. The current view is that the changes in the inter-relationship between the three main pillars of the intracellular metabolic triad: "Ca^{2+} mitochondria free radicals" is at the core of explaining the ageing process (Toescu 2005).

2. Relationship between Ca^{2+} homeostasis and mitochondrial status. My laboratory has been mainly studying the relationship between Ca^{2+} homeostasis and mitochondrial function in the aged neurones. The major proposition of CATA was that chronic minor disruptions of Ca^{2+} homeostasis, exerted over long period of time, are leading to major neuronal damage. One reason for this view was the emerging role, in the early 80s, of Ca^{2+} ions in mediating excitotoxic damage and eventual neuronal death. It is clear now that, in fact, in all neuronal types the values of resting free Ca^{2+} (Ca^{2+}_i) are not affected by age (Toescu et al. 2004; Verkhratsky & Toescu 1998). Also, the increase in the density of voltage-operated Ca^{2+} channels, generating an increased Ca^{2+} signal on neuronal stimulation is applicable mainly to the hippocampal CA1 neurones, but not to cerebellar granule neurones or to peripheral sympathetic neurones (Toescu et al. 2004). What is a consistent finding in all aged neurones is a significant delay of the rate at which Ca^{2+}_i returns to the resting levels following a stimulation paradigm. Two mechanisms have been proposed to explain such observations. One involves an increased participation of the intracellular, endoplasmic Ca^{2+} stores, through the process of Ca^{2+}-induced Ca^{2+} release (CICR) (Kelly et al. 2006; Toescu et al. 2004). The other process involves mitochondria. We and others have shown that in the aged cells, including neurones, the mitochondria are chronically depolarised (Hagen et al. 1997; Murchison et al. 2004; Xiong et al. 2002). Mitochondria are an important Ca^{2+} buffer, particularly at higher levels of stimulation, when Ca^{2+}_i in increased significantly, and the uptake of Ca^{2+} is dependent on the level of mitochondrial polarization. In experiments in which we have used fluorescent dyes to monitor simultaneously both the changes in Ca^{2+} and the level of mitochondrial depolarization (Xiong et al. 2004; Xiong et al. 2002) we have shown that almost all increases in Ca^{2+}_i are associated with a mitochondrial depolarization response, indicating the intimate participation of the mitochondria in cellular Ca^{2+} homeostasis. In the same experiments, we have shown that in the aged neurones there was a significant delay not only in the rate of Ca^{2+}_i recovery, but also in the capacity of mitochondria to repolarise following the stimulation-induced depolarization, and that these two parameters were closely correlated (Xiong et al. 2004; Xiong et al. 2002). A chronically depolarised mitochondrion, together with slower repolarisation capacity would result in an increased cytosolic Ca^{2+} load. In addition, a dysfunctional mitochondria compartment will decrease the amount of ATP available to extrude Ca^{2+} from the cytosol, a process that is dependent, ultimately, on the activity of plasma membrane or endoplasmic reticulum Ca^{2+} pumps (PMCA and SERCA respectively).

An interesting experimental observation, and which has very important implications for our understanding of the age-induced functional changes, was that the delay in the rate of Ca^{2+}_i recovery depended largely on the levels of stimulation (Toescu & Xiong 2004). With either non-specific depolarization or under glutamatergic stimulation, the aged neurones showed signs of dysfunctionality only at higher levels of stimulation. Thus, the aged neurones are perfectly capable of maintaining a good resting steady-state and able to respond to 'normal' levels of stimulation. Their susceptibility to damage became manifest only at higher, excessive levels of stimulation, leading to the concept of ageing as a state of reduced homeostatic reserve (Toescu 2005)

Ageing and Neurodegeneration

If there is a message to take home, from a basic science researcher to a clinician, that is that brain ageing is a normal physiological state, not a pathological state. It is a state Characterised by a gradual decline in the homeostatic reserve, defined as the capacity

Of neurones to oppose the destabilizing effects of metabolic stressors. The word "gradual" is of essence here, as the decrease in homeostatic reserve and the resultant functional changes take place over a long period (decades, in the case of humans). The role of the metabolic triad of Ca^{2+}-mitochondria-free radicals is central, but the aged-induced changes are entirely compatible with the maintenance of normal neuronal viability. In contrast, in various forms of neurodegeneration, such as Alzheimer's disease, Parkinson's disease, Huntingdon's or amyotrophic lateral sclerosis, in which ageing is an important risk factor, there are specific alterations, particularly a variety of mutations in nuclear-encoded proteins with mitochondrial (e.g., PINK1, Parkin) or metabolic (e.g., ApoE, presenilins) functions that are able to unbalance the decreased homeostatic reserve resulting in significant neuronal loss.

An important implication of the fact that ageing is due to functional rather than morphological changes, is that it opens the possibility that specific treatments with agents that target particularly the mitochondria might bring about a significant revival of the aged neurons, and bring back a sharper mind to the aged.

BIBLIOGRAPHY:

Brody, H. 1955 Organization of the cerebral cortex. III. A study of aging in the human cerebral cortex. J Comp Neurol **102**, 511-6.

Burke, D. M. & Mackay, D. G. 1997 Memory, language, and ageing. Philos Trans R Soc Lond B Biol Sci **352**, 1845-56.

Coleman, P. D. & Flood, D. G. 1987 Neuron numbers and dendritic extent in normal aging and Alzheimer's disease. Neurobiol Aging **8**, 521-45.

de Brabander, J. M., Kramers, R. J. & Uylings, H. B. 1998 Layer-specific dendritic regression of pyramidal cells with ageing in the human prefrontal cortex. Eur J Neurosci **10**, 1261-9.

Disterhoft, J. F. & Oh, M. M. 2006 Learning, aging and intrinsic neuronal plasticity. Trends Neurosci **29**, 587-99.

Foster, T. C. & Kumar, A. 2002 Calcium dysregulation in the aging brain. Neuroscientist **8**, 297-301.

Gallagher, M. & Rapp, P. R. 1997 The use of animal models to study the effects of aging on cognition. Annu Rev Psychol **48**, 339-70.

Hagen, T., Yowe, D., Bartholomew, J., Wehr, C., Do, K., Park, J. & Ames, B. 1997 Mitochondrial decay in hepatocytes from old rats: Membrane potential declines, heterogeneity and oxidants increase. Proc.Natl.Acad.Sci.USA **94**, 3064-3069.

Harman, D. 1956 Aging: a theory based on free radical and radiation chemistry. J Gerontol **11**, 298-300.

Hedden, T. & Gabrieli, J. D. 2004 Insights into the ageing mind: a view from cognitive neuroscience. Nat Rev Neurosci **5**, 87-96.

Hof, P. R. & Morrison, J. H. 2004 The aging brain: morphomolecular senescence of cortical circuits. Trends Neurosci **27**, 607-13.

Jacobs, B., Schall, M., Prather, M., Kapler, E., Driscoll, L., Baca, S., Jacobs, J., Ford, K., Wainwright, M. & Treml, M. 2001 Regional dendritic and spine variation in human cerebral cortex: a quantitative golgi study. Cereb Cortex **11**, 558-71.

Kelly, K. M., Nadon, N. L., Morrison, J. H., Thibault, O., Barnes, C. A. & Blalock, E. M. 2006 The neurobiology of aging. Epilepsy Res **68 Suppl 1**, S5-20.

Khachaturian, Z. S. 1984 Towards theories of brain aging. In Handbook of Studies on Psychiatry and Old Age (ed. D. Kay & G. Burrows), pp. 7-30. Amsterdam: Elsevier. Malenka, R. C. & Bear, M. F. 2004 LTP and LTD: an embarrassment of riches. Neuron **44**, 5-21.Ming, G. L. & Song, H. 2005 Adult neurogenesis in the mammalian central nervous system. Annu Rev Neurosci **28**, 223-50.

Miquel, J., Economos, A. C., Fleming, J. & Johnson, J. E., Jr. 1980 Mitochondrial role in cell aging. Exp Gerontol **15**, 575-91.

Morrison, J. & Hof, P. 1997 Life and death of neurons in the aging brain. Science **278**, 412-419.

Murchison, D., Zawieja, D. C. & Griffith, W. H. 2004 Reduced mitochondrial buffering of voltage-gated calcium influx in aged rat basal forebrain neurons. Cell Calcium **36**, 61-75.

Reuter-Lorenz, P. 2002 New visions of the aging mind and brain. Trends Cogn Sci **6**, 394.

Rosenzweig, E. S. & Barnes, C. A. 2003 Impact of aging on hippocampal function: plasticity, network dynamics, and cognition. Prog Neurobiol **69**, 143-79.

Terry, R. D. & Katzman, R. 2001 Life span and synapses: will there be a primary senile dementia? Neurobiol Aging **22**, 347-8; discussion 353-4.

Toescu, E. C. 2005 Normal brain ageing: Models and Mechanisms. Philos.Trans.R.Soc.Lond. **360**, 2347-54.

Toescu, E. C., Verkhratsky, A. & Landfield, P. W. 2004 Ca2+ regulation and gene expression in normal brain aging. Trends Neurosci **27**, 614-20.

Toescu, E. C. & Xiong, J. 2004 Metabolic substrates of neuronal aging. Ann N Y Acad Sci **1019**, 19-23.

Verkhratsky, A., Mattson, M. P. & Toescu, E. C. 2004 Aging in the mind. Trends Neurosci **27**, 577-8.

Verkhratsky, A. & Toescu, E. 1998 Calcium and neuronal ageing. Trends Neurosci **21**, 2-7.

Vreugdenhil, M. & Toescu, E. C. 2005 Age-dependent reduction of gamma oscillations in the mouse hippocampus in vitro. Neuroscience **132**, 1151-7.

Xiong, J., Camello, P. J., Verkhratsky, A. & Toescu, E. C. 2004 Mitochondrial polarisation status and [Ca2+]i signalling in rat cerebellar granule neurones aged in vitro. Neurobiol Aging **25**, 349-59.

Xiong, J., Verkhratsky, A. & Toescu, E. C. 2002 Changes in mitochondrial status associated with altered Ca2+ homeostasis in aged cerebellar granule neurones in brain slices. J.Neurosci **22**, 10761-10771.

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NON-COGNITIVE SYMPTOMS OF DEMENTIA

In 1907, Alois Alzheimer described a complex clinical picture of disturbance in cognitive, behaviour and affect. The cognitive aspects of AD are well understood: progressive loss of memory and execution function, coupled with progressive increases in aphasia and apraxia, are considered hallmarks of the disease and correlations between these signs and the neuropathologic signs has been well established as well.

More recently, a substantial body of clinical neuroscience research has documented the underlying pathophysiology of the non-cognitive symptoms of AD, such as depression, psychoses and circadian disruption (Finkel 1996). Though recognized, the importance of non-cognitive symptoms was still diminished some time, by being referred to as secondary or concomitant symptoms of dementia.

Today they are not only seen as core symptoms along with the cognitive impairment of dementia, but they are being recognized as leading risk factors driving the need for log-term care.

World Psychiatric Association and the International Psychogeriatric Association elaborated an international consensus deciding that BPSD - 'Behavioral and Psychological Symptoms of Dementia' is the most appropriate term to describe the diverse psychopatology that may occur in dementia. The revised actual definiton of BPSD is: "a term used to describe a heterogeneous range of psychological reactions, psychiatric symptoms, and behaviors occurring in people with dementia of any etiology."

Today it is recognized that BPSD are very common and significant, that any symptom can occur during any stage in dementia (including MCI) and that at certain stages, virtually all pacients demonstrate some type of BPSR (Reisberg).

BPSD proved to be a distinct entity, with a different phenomenology, that can be differentiated from other late-life psychopathology and can be identified in different types of dementia. There is an emerging understanding of the multifactorial etiology of BPSD, supporting the notion that a range of biopsychosocial factors may be involved.

The following comparable syndromes were identified in different studies as being stable over time:

- aggressive behaviour (aggressive resistance, active physical aggression: aggression toward others, aggression to him or herself, aggression toward objects, physical threats, verbal aggression)
- depression (sad appearance, anxiety, crying, guilt, saying gloomy things)
- apathy (social and emotional withdrawal, loss of interests, tiredness)
- motor hyperactivity (pacing/aimless walking, handling objects inappropriately, increased confusion and motor agitation during the evening
- psychoses (hallucinations, unusula thoughtscontent, suspiciousness)

There are discussed specific diagnostic criteria, as well as the main reliable and valid scales for assessment of BPSD in different dementias (BEHAVE-AD, NPI, Cornell Scale for Depression in Dementia, Cohen-Mansfield Agitation Inventory, The Frontal Benavioral Inventory).

The last part of the lecture presents the management of neuropsychiatric aspects in dementia, focussing on the alliance and the intensive work with carers, on non-pharmacological interventions and on the general principles of pharmacologic management of individuals with BPSD.

Pharmacological interventions should be used for treatment of BPSD in dementia patients only when non-pharmacological treatments are not feasible or have failed. In many cases non-pharmacologic management can be used in combination with pharmacotherapy in order to amplify the results and to minimize the required doses.

Non-pharmacologic management strategies are largely based on changing caregiver behaviour (teaching them the four Re: Reassure, Reorient, Remind, Redirect) and/or restructuring the environment in a varieties of ways in order to decrease problematic behaviours. These strategies include: changes in the physical environment, patient occupational-activities by participation at day-care activites, family caregivers activities, (support groups, educational programms, family counseling, respite care, telephone helplines etc.). Music, simulated sounds of nature, bright lights, creation of a homelike settings in institutions have all been recommended as means to diminish behavioural disturbance in patients with more advanced dementia.

Pharmacological management that are useful in dementias address the underlying disease process, any comorbid medical conditions that require therapy and treatment of BPSD that fail to respond or respond inadequately to nonpharmacologic interventions.

Use of pharmacologic agents in elderly and demented individuals needs expertise. These agents have powerful effects in reducing BPSD but they may have marked side effects. A specific behavioural target symptom has to be chosen and the response should be carrefully monitored.

Starting doses should be one-third to one-half those recommended in younger adults, increasing the dose has to be slowly, and escalating the dose until an adequate beneficial response occurs or tolerability limits further dose increases. Partial responses may be oftne acceptable if complete improvement of a psychiatric symptom cannot be achieved without unacceptable side effects.

No pharmacologic agent has been approved specifically for the management of behavioral disturbances in dementia, and treatment is guided by clinical trials and clinical experience.

There are presented the most efficacious agents and with the less side effects in elderly that are nowadays recommended for the tratment of agitation, psychoses (hallucinations and delusions), depression, anxiety, apathy, insomnia, sexual aggression. There are also discussed particular aspects of BPSD treatment in dementia with Lewy bodies, Vascular dementia, Parkinson Dementia.

Effective management of neuropsychiatric symptoms may reduce caregiver exagerated stress, may avoid patient hospitalization or may delay residential placement improving the quality of life of both patient and family.

BIBLIOGRAPHY:

1. Sanford I. Finkel, (1996), Behavioral and psychological signs and symptoms of dementia: Implications for research and treatment. *International Psychogeriatrics*, 8 (Supl.3) 215-552 **2.** BPSD: New terminology [Editorial] (1997). *International Psychogeriatrcs*, 9, 227
3. Jeffrey L. Cummings, *The Neuropsychiatry of Alzheimer's Disease and Related Dementias* (2003), Martin Dunitz, 1-23, 281-301
4. Barry Reisberg (1989), Behavioral symptoms in AD Phenomenology and Treatment, *Journal of Clinical Psychiatry*, 48, (Suppl.), 9-15
5. German E. Berrios, John R. Hodges (2000), *Memory Disorders in Psychiatric Practice*, 75-101
6. Barry D, Lebowitz, (2000), BPSD A clinical and Research Update, *International Psychogeriatrics*, vol.12,(Auppl.1), 19-21

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DAMAGE OF NEURONAL TISSUE: THERAPEUTIC CONSIDERATION

(from the biochemical point of view; mitochondrial abnormalities, kynurenine system etc.)

Mitochondria and neurodegeneration

The mitochondria have several important functions in the cell. A mitochondrial dysfunction causes an abatement in ATP production, oxidative damage and the induction of apoptosis, all of which are involved in the pathogenesis of neurological disorders.

During energy production, most of the O_2 consumed by the mitochondria is reduced fully to water, but 1-2% of the O_2 is reduced incompletely to give the superoxide anion (O_2^-). If the function of one or more respiratory chain complexes is impaired for any reason, the enhanced production of free radicals further worsens the mitochondrial function by causing oxidative damage to macromolecules, and by opening the mitochondrial permeability transition pores thereby inducing apoptosis. These high-conductance pores offer a pathway which can open in response to certain stimuli, leading to the induction of the cells' own suicide program. This program plays an essential role in regulating growth and development, in the differentiation of immune cells, and in the elimination of abnormal cells from the organism. Both failure and exaggeration of apoptosis in a human body can lead to disease. The increasing amount of superoxide anions can react with nitric oxide to yield the highly toxic peroxynitrite anion, which can destroy cellular macromolecules. Senescence is accompanied by a higher degree of reactive oxygen species production, and by diminished functions of the endoplasmic reticulum and the proteasome system, which are responsible for maintenance of the normal protein homeostasis of the cell. In the event of a dysfunction of the endoplasmic reticulum, unfolded proteins aggregate in it, forming potentially toxic deposits which tend to be resistant to degradation. They are key components in the processes of development, ageing and cell death (both apoptotic and necrotic).

A mitochondrial dysfunction and oxidative damage play roles in the pathogenesis of numerous disorders, e.g. Parkinson's disease (PD), Alzheimer's disease (AD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), Wilson's disease, Friedreich's ataxia, multiple sclerosis and a number of inherited disorders of the mitochondrial genome, the mitochondrial encephalomyopathies (e.g. Leber's disease /with optic atrophy and dystonia/, MELAS, MERRF, Leigh's disease, Kearns-Sayre syndrome). The list of mitochondria-related diseases is growing rapidly: cancer, heart failure, diabetes, obesity, ischemia-reperfusion injury, atherosclerosis, certain liver diseases and asbestosis. They all share the common features of disturbances of the mitochondrial Ca^{2+}, ATP or reactive oxygen species (ROS) metabolism.

Generation of free radicals. Oxidative damage

The loss (steal) of electrons is called oxidation. The adducts generated in this way are called free radicals (oxidizing agents). A characteristic of these radicals is their bias toward donation of their electron to other molecules, causing oxidative damage.

The mitochondrial respiratory chain is one of the major sources of damaging free radicals in human organism. Unpaired electrons escaping from the respiratory complexes (mainly from complexes I and III) can lead to the formation of superoxide anions (O_2^-) by the interaction with O_2. For physiological or pathological stimuli, the activation of excitatory amino acid receptors (N-methyl-D-aspartate, NMDA) leads to intracellular Ca^{2+} accumulation and nitric oxide synthase (NOS) activation, gaining NO. An increasing amount of O_2^- interacts with NO to yield the highly toxic peroxynitrite anion ($ONOO^-$), while O_2^- may spawn the production of hydrogene peroxide (H_2O_2) spontaneously or through the action of manganese superoxide dismutase (MnSOD).

$O_2^- + NO \longrightarrow ONOO^-$

$O_2^- \xrightarrow{SOD} H_2O_2 + O_2 \qquad (2O_2^- + 2H^+ \longrightarrow H_2O_2 + O_2)$

Under physiological condition, H_2O_2 is broken down by glutathione peroxidase, but if it is formed in excess, it can react with transition metal ions (Fe^{2+} or Cu^{2+}) in the Fenton reaction, to generate the other highly reactive toxic radical, the hydroxyl radical (OH^-).

$H_2O_2 + Fe^{2+} \longrightarrow Fe^{3+} + OH^- + OH^-$

These reactive radicals destroy cellular macromolecules, including DNA, lipids and proteins. Protein oxidation and nitration may be a crucial importance in the cell cycle. Oxidized and nitrated proteins preferentially undergo fast proteolytic degradation. O_2^- itself is moderately damaging, but highly reactive. The mitochondria (the electron transport chain) are one of the major sources of free radicals, but other pathways are also known to produce radicals (e.g. xanthine oxidase, monoamine oxidase, cytochrome P450, NOS, myeloperoxidase and NADPH oxidase). Major targets of ROS production are the microglia, neutrophils and macrophages.

Although the mitochondria lack protective histones, they have DNA repair machinery (which is entirely nuclear encoded) to protect against oxidative and nitrative/nitrosative (caused by NO and $ONOO^-$) damage. There are 2 major groups in their defense system: enzymes (superoxide dismutase, catalase, peroxidase, peroxiredoxin and some supporting enzymes) and low molecular weight antioxidants; the indirect-acting antioxidants (e.g. chelating agents) and direct-acting compounds (e.g. glutathione, NADPH and exogenous agents from dietary sources: ascorbic acid, lipoic acid, polyphenols and carotenoids). However, these protective mechanisms are not particularly efficient.

Astrocytes are more resistant than neurons to $ONOO^-$, which may be due to their higher GSH content, which functions as a defense tool in neutralizing NO radicals. They can increase glycolysis to maintain their energy homeostasis, as opposed to neurons. Moreover astrocytes even donate GSH precursors to neurons. They are presumed to release a factor, termed "extracellular superoxide dismutase" to protect released GSH from degradation (8, 23).

Cells have an adaptive, restorative repertoire against oxidative stress, such as

the enhanced production of defensive enzymes, an increase in glycolysis, and the activation of genes encoding transcription factors and structural proteins.

Effects of reactive radicals

A shift in the balance between ROS generation and the elimination of overproduction or decreased detoxification is denoted as "oxidative stress", which is associated with chronic diseases. The mitochondria are thought to be both generators of ROS and targets of ROS attack. The main source of ROS formation, as discussed above, is the mitochondria in the course of electron transport in the oxidative phosphorylation chain. During the electron flow, a small proportion of the electrons (2%) leak out and generate O_2^- and H_2O_2.

The reaction of NO with O_2^- yields the highly toxic $ONOO^-$, which can cause oxidative and nitrative damage to the mitochondria and ultimately lead to cell death pathways . The mitochondrial respiratory chain is particularly sensitive to both NO and ONOO -mediated damage. Besides causing damage to the respiratory chain complexes (mostly complexes I and IV), $ONOO^-$ may exert its toxic effect through the induction of mtPTP and the activation of caspase-dependent and/or caspase-independent pathways. In contrast, NO itself can either induce or inhibit mtPTP.

$ONOO^-$ also causes DNA damage and subsequent overactivation of poly(ADP-ribose) polymerase (PARP) in order to repair the genetic fault. The function of the latter enzyme is a double-edged sword, as it involves at the same time the consumption of ATP and NAD^+, the depletion of which can contribute to cell death. Whereas the activation of PARP-1 caused by mild genotoxic stimuli may facilitate DNA repair and cell survival, irreparable DNA damage triggers apoptotic or necrotic cell death. In apoptosis, early PARP activation may assist the apoptotic cascade (e.g. by mediating the translocation of the apoptosis-inducing factor (AIF) from the mitochondria to the nucleus or by inhibiting the early activation of DNases). However, in more severe oxidative stress situations, excessive DNA damage causes the overactivation of PARP-1, which incapacitates the apoptotic machinery and switches the mode of cell death from apoptosis to necrosis.

Protein nitration can modify the protein function, and it is nowadays thought to be involved in the pathomechanism of several diseases, for instance PD, AD, and HD. On the other hand, it must not be forgotten that NO is a gaseous, highly diffusible, important biological messenger, which plays a prominent role in the communications between cells during the normal functioning of the central nervous system (CNS). However, an increasing amount of evidence indicates that NO modulates neurotoxin-induced cell damage and is involved in neuronal cell death in PD. There are three clearly identified isoforms of NOS, primarily produced by neurons (nNOS), in microglial cells and macrophages (iNOS) and in endothelial cells (eNOS). However, there is now evidence that a fourth, less clearly identified, Ca^{2+}-sensitive isoform of NOS also exists, located at the matrix face of the inner membrane of the mitochondria (mtNOS), which may be a variant of nNOS. It is known that NO competes with O_2 for the O_2-binding site in COX in complex IV. In this way, NO inhibits electron transfer to O_2 and increases the rate of production of O_2^- and H_2O_2 . Elevation of the intramitochondrial Ca^{2+} concentration infers an increased mtNOS activity leading to decreases in mitochondrial O_2 consumption and in mitochondrial transmembrane potential, and also to Ca^{2+} accumulation, and ultimately to a decrease in ATP formation . Overall, it may be assumed that the redox states of the mitochondria are the key components in the regulation of various basic cellular functions, such as mitogen-activated protein kinase cascade activation, ion transport, Ca homeostasis and apoptosis program activation.. However, the redox potentials are strongly dependent on ROS.

The kynurenine system

The kynurenine pathway (KP) is the main pathway of the tryptophan (TRP) metabolism, which is primarily responsible for nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP). The central substance of this pathway is kynurenine (KYN) produced from TRP via a transition product, formly-KYN, with the aid of TRP- or indolamine-2,3-dioxygenase (TDO or IDO). KYN is a precursor of the neuroprotective kynurenic acid (KYNA) and the neurotoxic quinolinic acid (QUIN). KYNA is formed directly from L-KYN by irreversible transamination and this compound is a broad-spectrum antagonist of the excitatory amino acid (EAA) receptors, which can act primarily at the strychnine-insensitive glycine-binding site of the NMDA receptors. Moreover, KYNA non-competitively blocks the alpha7-nicotinic acetylcholine receptors, and can therefore take part in glutamatergic and nicotinergic neurotransmission. We found that kynurenine administered together with probenecid markedly inhibits pentylenetetrazol-induced seizures. CA3 stimulation-evoked population spike activity was recorded from pyramidal layer of area CA1 of the rat hippocampus. In another series of behavioural experiments, water maze and open-field studies were carried out to test the presumed protective effect of KYN+probenecid pretreatment against pentylenetetrazol-induced seizures. Furthermore, administration of KYN produced significant increase in the normal corticocerebral blood flow (cCBF) in rabbits; the peak values were recorded at the dose of 1 mg/kg (187% at 120 and 150 mins). The cCBF- improving effect of KYN was immediate and highly pronounced also in rabbits with carotid occlusion. Pretreatment with either atropine or L-NAME prevented KYN-induced enhancement of the normal and the ischemic cCBF alike. It is suggested that the cCBF-increasing effect of KYN might be mediated by activation of cholinergic and nitric oxide pathway. In another experiment densitometric analysis proved that, in consequence of 6-OHDA treatment, not only tyrosine hydroxylase (TH) but also KAT-I immunoreactivity diminished considerably in the remaining substantia nigra pars compacta neurons in rats. It is hypothesized that biochemical approaches which increase KYNA content of the central nervous system might prevent the deleterious effect of 6-OHDA and, supposedly, also the neuronal degeneration characterizing Parkinson's disease.

References:

[illegible]

[illegible]

[illegible]

[illegible]

Sas, K., Robotka, H., Toldi, J., Vécsei, L.: Mitochondria, metabolic disturbances, oxidative stress and the kynurenine system, with focus on neurodegenerative disorders.
J. Neurol. Sci. in press, 2007.

Vécsei, L. (ed.): Frontiers in Clinical Neuroscience. Neurodegeneration and Neuroprotection. (AEMB VOL 541), Kluwer, New York, 2004.

Vécsei, L (ed.): Kynurenines in the Brain: From Experiments to Clinics. NOVA, New York, 2005.

THE SOCIETY FOR THE STUDY OF NEUROPROTECTION AND NEUROPLASTICITY

NEUROTRAUMA SESSION

DAY 2 **21** March

2007, Wednesday

SPEAKERS IN ALPHABETICAL ORDER:

Alekseenko Yuri (Belarus): Early management of mild traumatic brain injury

Gerstenbrand Franz (Austria): Traumatic brain injury, biomechanic aspects and classification

Mureşanu Dafin (Romania): Neuroprotection and neuroplasticity in traumatic brain and spinal cord injury

Vos Pieter (Netherlands): Biochemical markers of traumatic brain injury

Klauv von Wild (Germany): Prediction of outcome in traumatic brain injury

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EARLY MANAGEMENT OF MILD TRAUMATIC BRAIN INJURY

About 80-90% of traumatic brain injury incidents are classified as mild traumatic brain injury (MTBI). MTBI results from a number of causes, including falls, interpersonal violence, road accidents, and sport-related events, although the proportion of these causes depends on the population and country, gender and age group. MTBI may present with varying neurologic findings and sometimes be accompanied by alcohol or drug intoxication, concomitant neurologic or somatic disorders that should be encountered during the evaluation. The diagnosis of MTBI is usually complicated, because the routine neurological examination of patients after the trauma does not usually reveal any visible neurological changes. At the same time the majority of MTBI symptoms including headache are mainly of a subjective character. Management decisions may be challenging in confused or amnestic patients at the place of accident or the emergency department.

Unfortunately, such terms as concussion, mild head injury, mild traumatic brain injury, cerebral concussion, and post concussion syndrome are often used interchangeably to describe the physical injury itself as well as its immediate and later symptomatic consequences. Intracranial complications of MTBI are not frequent but potentially life-threatening, and may require neurosurgical intervention (less or about 1%). That is why exclusion of minimal chance of such dangerous neurosurgical intracranial complications in large numbers of patients remains a key problem of MTBI management.

There are more than 40 different diagnostic guidelines for MTBI, some of which relate specifically to sports injury, admission policy, imaging, neuropsychological assessment, and management of children. Current MTBI definition and classification is based on admission Glasgow Coma Scale (GCS), trauma history, including the duration of loss of consciousness (LOC) and post-traumatic amnesia (PTA), age, neurological signs and symptoms, and risk factors for intracranial complications. MTBI is defined as the consequence of a blunt (non-penetrating) impact with sudden acceleration, deceleration, or rotation of the head (ICD-10 codes: S-02, S-04, S-06, S-07, S-09) and GCS score of 13-15 at the time of hospital admission. The time between the accident and hospital admission can influence the GCS score. If the patient is unable to provide a reliable history, information from witnesses or family members will be helpful. The exact mechanism of head injury as well as direct evidences of head trauma (abrasions, bruises) should be considered in MTBI diagnostic protocol.

Important points of early management include the assessment of LOC and PTA duration, signs of intoxication and other injuries. Brief disturbance or LOC of less than 30 minutes and/or PTA duration of up to 24 hours, with or without other neurological abnormalities, are compatible with the diagnosis of MTBI. At the same time MTBI outcome is considered good (mortality 0.1%) if the duration of LOC is less than 30 minutes and/or PTA less than 1 hour, especially in the absence of additional risk factors.

A potential pitfall in the management of the patient with MTBI is an assumption that this injury is entirely responsible for the overall clinical picture. A comprehensive approach requires initial consideration of the reversible causes of altered mental status including hypoperfusion, hypotension, hypoxemia, hypoglycemia, and drug toxicity. Special emphasis on possible antecedent events, such as syncope, transient ischemic attack, orthostasis, or dysrhythmia, is needed, particularly in the case of an elderly patient.

Symptoms of MTBI may or may not persist, for varying periods of time. There are three categories of possible acute MTBI symptoms: a) physical, b) emotional, c) cognitive and behavioral - which, along or in combination, may produce a functional disability. Physical symptoms include headache, nausea, vomiting, dizziness, blurred vision, fatigue, sleep disturbances but not those that can be accounted for by peripheral injury or other causes. Cognitive deficits (attention, concentration, perception, memory, speech/language, or executive function), behavioral changes and emotional lability exclude symptoms that can be accounted for by emotional state or psychological reaction or other causes. There are some controversies in regard to exact origin and interpretation of such symptoms. All these signs are usually intermixed with signs and symptoms of injuries to the peripheral vestibular system and to the head and neck as well as with symptoms of psychological state (preinjury and postinjury) of the patient. Headache should be considered as a phenomenon graduated in intensity and duration but at the same time as one of the most important signs of MTBI. Computed tomography (CT), magnetic resonance imagine (MRI) or routine neurological evaluation in MTBI may be normal.

Natural course of recovery is quite different for various groups of traumatic disorders. MTBI is characterized by trauma-induced brief disorders of consciousness, changes of memory and mental functions, generally lasting less than 24 hours, and a complex of physical, cognitive and behavioural symptoms usually recovering within 2-3 weeks - 1-3 month; by 3 months 75% of patients will be symptom-free. In young and preinjury healthy patients the resolving of main physical symptoms can take about 1-2 weeks. Such symptoms as headache, dizziness, anxiety, and impaired cognition and memory may persist after MTBI. This constellation of symptoms, known as postconcussive syndrome (PCS), affects more than 60% of patients 1 month after the injury and 15% at 1 year.

The primary goal of initial management in MTBI is to identify the patients at risk of intracranial abnormalities and especially those that may need neurosurgical intervention. Use of a clinical decision scheme based on risk factors may facilitate this process. Posttraumatic intracranial complications can be divided into two groups: 1. Intracranial abnormalities that often need neurosurgical intervention (extracerebral haematoma, depressed skull fracture, growing skull fracture, secondary haemorrhagic contusion, subdural effusions, malignant brain oedema with diffuse brain swelling). 2. Conservatively treated intracranial lesions (contusion zones, brain oedema, diffuse axonal injury, small haemorrhages, traumatic subarachnoid haemorrhage, pneumocephalus). The intracranial haemorrhage (haematoma) is potentially the most threatening complication after MTBI and can be easily identified with CT, which should

be carried out urgently. CT is very sensitive in the detection of extracerebral haematoma and other intracranial abnormalities, although no formal CT classification for MTBI exists. CT is a standard for the detection of life threatening (and other intracranial) abnormalities after MTBI and is recommended in those with documented LOC and/or PTA. It is considered mandatory in all patients with certain clinical findings (GCS 13-14, or GCS 15 in the presence of risk factors).

There are several symptoms, signs and risk factors associated with an increased risk of intracranial injury: GCS score at the time of hospital admission, presence of persistent anterograde amnesia, retrograde amnesia longer than 30 minutes, trauma above the clavicles including facial or cranial soft tissue injury, and clinical signs of skull fracture (skull base- or depressed skull fracture), severe headache, nausea, vomiting (2 times), focal neurological deficit, cranial nerve deficit, motor deficit, dysphasia, seizure, age, coagulation disorders, high-energy accident (dangerous mechanism of injury) and intoxication with alcohol/drugs.

MRI may be of value for the detection of structural brain damage in patients without CT abnormalities, end especially in those with long-term complaints. Skull radiography is not recommended for the evaluation of MTBI because of its insufficient value in the detection of intracranial abnormalities in patients with MTBI but it may be in use for skull fracture detection if CT availability is limited.

During the initial stage of management any patient with trauma should be evaluated for surgical trauma with the assessment of the airways, breathing, and circulation, and the cervical spine. A neurological examination is obligatory and should include the evaluation of the following parameters: consciousness level, presence of anterograde or retrograde amnesia and/or disorientation, higher cognitive functions, presence of focal neurological deficit (asymmetrical motor reactions or reflexes, unilateral paresis or cranial nerve deficit), pupillary responses, blood pressure, and pulse rate, presence of frontal lobe signs, cerebellar symptoms, or sensory deficits. Accurate history taking (including medication), preferably with information obtained from a witness of the accident or medical personnel, is important to ascertain the circumstances (mechanism of injury) under which the accident took place and to assess the duration of LOC and amnesia.

Hospitals should have a protocol for resuscitation and triage of patients with MTBI. Category 2 (GCS 15 + risk factors) and 3 (GCS 13-14 ± risk factors) patients should be admitted to a neurotrauma centre. CT is recommended for category 1 patients (GCS 15, LOC < 30 min, PTA < 60 min, no risk factors) and is mandatory for all category 2 and 3 patients. If CT findings are normal, adult category 1 patients can be discharged and head injury warning instructions should be given to the patient and family members. Compliance is greater if both verbal and written instructions are given. A repeated CT should be considered if the admission CT findings were abnormal or if risk factors are present.

The main goal of clinical observation is to detect, at an early stage, the development of extradural or subdural haematoma or diffuse cerebral oedema. A secondary goal is to determine the duration of PTA. A distinction should be made between disorientation and amnesia because the two do not always disappear at the same time. A complete neurological examination is mandatory after admission and should include assessment of the GCS. Repeated neurological examination should be carried out, its frequency being dependent on the clinical condition of the patient. The patient should be examined every 30 minutes and if no complications or deterioration occurs, every 1-2 hours. If deterioration occurs, possible intracranial causes should be evaluated with repeated CT.

No strict recommendations can be given for the need for or duration of bed rest.

Early graded resumption of activities (including return to work) is probably the best strategy taking into account the patient's age, dominated symptoms and concomitant neurological and somatic disorders.

It is recommended that all patients in MTBI category 3 who have been admitted to hospital should be seen at least once in the outpatient clinic in the first two weeks after discharge. Patients with head injury who are discharged immediately provided with instructions should contact their general practitioners, who can decide about referring the patient to the neurologist if complaints persist.

Patients with MTBI have only a slightly increased risk of developing post-traumatic seizures including early (occurring in the first week) and late post-traumatic seizures. Early and immediate seizures are likely to have a different pathogenesis than late seizures; early post-traumatic seizures are thought to be a nonspecific response to the physical insult. Prophylactic antiepileptic treatment in this case is not warranted. If recurrent seizures occur, treatment is probably necessary and alternative explanations (i.e., delayed haematoma, Wernicke-Korsakoff syndrome, alcohol withdrawal or electrolyte disturbances) should be taken into account.

Concomitant mild and moderate alcohol intoxication (AI) seems to produce a complex dual effect on the spectrum of clinical symptoms of MTBI. Patients with AI demonstrated more extensive and frequent disorders of consciousness and amnesia in comparison with MTBI patients without AI. Patients with AI are less able to confirm such disturbances of consciousness and memory by themselves. MTBI patients with AI demonstrated a relatively favourable recovery from subjective symptoms of autonomic dysfunction and headache. AI seems to decrease the "concussion threshold", simultaneously producing some neuroprotective influence on brain mechanisms and contributing to patients' recovery after the MTBI, though the spectrum of symptoms after the trauma may be wider. Blood alcohol concentration should be taken into account. Alcohol concentration should be calculated for the moment of the accident.

Different groups of medications may be used in acute and remote periods of MTBI (simple analgesics, beta-blockers, vasoactive and neuroprotective drugs, antidepressants, antiepileptics, major tranquillizers and benzodiazepines, etc) according to circumstances and indications. But there is no consensus in regard to optimal evidence-based pharmacological treatment in MTBI patients. The majority of all these medications can cause some adverse effects and impair recovery. Early post-traumatic headaches are common and should be treated with simple analgesics, though these are not always as effective as just the passage of time. Paracetamol with or without codeine or non-steroidal anti-inflammatory drugs can be helpful. When headaches persist for longer, traditional headache prophylaxis may be required. Daily analgesia should be avoided to prevent the emergence of rebound headaches. Early post-traumatic global or hemicranial headache which persists and worsens should prompt CT brain scanning just to rule out the outside possibility of subdural haematoma, but delayed onset of headache (2 or 3 weeks after injury) rarely demands investigation. Localized head pains may require specific imaging or referral to ophthalmologist or otolaryngologist. Early localized neck muscle tenderness is common when there is associated whiplash and it will usually settle spontaneously.

References:

1. Vos PE, Alekseenko Y, Battistin L, Birbamer G, Gerstenbrand F, Potapov A, Prevec T, Stepan ChA, Traubner P, Twijnstra A, Veesei L, von Wild K. Mild traumatic brain injury. European Handbook of Neurological Management. Blackwell Publishing, 2006; Ch. 16: 207-223.
2. Gerstenbrand F, Stepan CH. Mild traumatic brain injury. Brain Injury 2001; 15(2):95-97.

3. Mild Traumatic Brain Injury Committee. Definition of mild traumatic brain injury. J Head Trauma Rehabil 1993; 8(3):86-87.
4. Alexander MP. Mild traumatic brain injury: pathophysiology, natural history, and clinical management. Neurology 1995; 45(7):1253-1260.
5. Anderson T, Heitger M, Macleod AD. Concussion and mild head injury. Practical Neurology 2006; 6(6): 432-357.
6. Andrews M, Bruns J. Early Evaluation and Management of Mild Traumatic Brain Injury. Applied Neurology, June 17 2006; CMP Medica.
7. de Kruijk JR, Twijnstra A, Meerhoff S, Leffers P. Management of mild traumatic brain injury: lack of consensus in Europe. Brain Injury 2001; 15(2):117-123.

Alekseenko Y, Luchanok U. Posttraumatic headache in patients with mild traumatic brain injury. The Classification and Diagnosis of Headache Disorders; Jes Olesen ed. Oxford University Press, Oxford, 2005: 203-206

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TRAUMATIC BRAIN INJURY, BIOMECHANIC ASPECTS AND CLASSIFICATION

Worldwide as an attribute to the modern way of life the increased number of traumatic brain injury (TBI) can be observed. Improved standards of living, traffic, modemisation, industrialization, development and advancement of the society must be accused for this development. Between the age of 20 to 35 the most frequent cause of death is traumatic brain injury.

Depending on the direction and the intensity to the impact of the head an open or a closed cerebral trauma has to be differentiated. Based on clinical symptomatology, neuropathological findings and the results of modern neuro-imaging methods (living pathology-Grcevic) three types of TBI have to be differentiated: The linear outer brain trauma with lesions on the surface of the brain (Coup, Contre Coup), the linear inner brain trauma and the rotational brain trauma. The linear inner brain trauma has to be divided in the linear inner upper brain trauma with lesions around the ventricle system (butterfly type - Grcevic) and the linear inner lower brain trauma (Lindenberg) the most dangerous type of TBI , with lesions in the mid brain region and the surrounding brain areas. The rotational brain trauma causes intracerebral haematoma and dilaceration of brain tissue mostly in the inner capsle and the basal ganglia as well as extracerebral haematomas, intracranial haematomas.
More then one impact with a multifocal influence on the brain is possible.

The documentation of an impact on the head using the Innsbruck Impact Scheme allows to analyze the biomechanical forces on the brain. The localization and the grade of primary traumatic brain defects can be calculated. In the severity of TBI the modern classification divided between mild, moderate, severe and severest TBI.

Regarding the anatomical and histological changements four forms of traumatic lesions of brain tissue can be differentiated. The primary brain lesions resulting at the moment of the impact are irreversible. Secondary brain lesions as sequencies of circulatory deficit in the Penumbra of the primary defect cause local tissue lesions. hypoxia and/or hypoxemia are responsible for diffuse and regional brain tissue lesions.

Tertiary lesions, developing mostly in a longer posttraumatic course are responsible for encephalopathia, pontine myolinolysis, myelopathia and polyneuropathia, originated by malnutrition, malabsorption, avitaminosis and the bed rest syndrome. As quartery lesions developing in posttraumatic stage, sometimes months till years afterwards a hydrocephalus occlusus, mengingo- encephalitis and brain abcess can be observed. As complications contractions of the bigger joints, periarticular ossification, decubitus and lesions of peripheral nerves have to be kept in mind.

In the acute state every patient with a TBI needs exact neurological controls with different additional examinations depending on the grade, but obligatory in severe and severest conditions. A neuromonitoring is necessary for every patient.

The most dangerous and acute complications of TBI are brain oedema and intracraniel haematoma, both with an increase of the intracranial volume followed by tentorial herniarion, sometimes by foraminal herniation, accompanied by an acute mid brain syndrome and acute bulbar brain syndrome (F.Gerstenbrand, C.H.Lücking). In severe conditions a traumatic apallic syndrome, unfortunately in English literature called vegetative state, can develop (F.Gerstenbrand) .
Never to forget is an accompagnied damage of the cervical spine together with a spinal cord trauma.

Every patient with the TBI needs an acute therapy independently to the grade. The treatment programme has to be accompanied by a monitoring system, essentially including MTBI (Vos et al). In severe and severest form of a TBI a neurosurgical consultation is obviously necessary. The treatment of TBI has to start out of the hospital, already on the place of the accident , initiated with measures to care the vital functions. Severest TBI patients have to be transferred immediately in a modern equipped ICU.

Every patient with TBI, independent to the grade of the brain lesions, needs a neurorehabilitation with a consequent programme. A special centre with trained personal under the responsibility of a neurologist is necessary. The neurorehabilitation has to start immediately, already in the admitting hospital. A consequent programme of modern neurorehabilitation can reduce not only suffering and the individuality of young patients, it reduces the expenses of the health system in a considerable rate.

BIBLIOGRAPHY

1. Birbamer G., Gerstenbrand F.,Grcevic N., 1990, Klassifikation d.schweren zerebralen Traumas
Acta Chir Austr. 31,20-22
2. Gerstenbrand F., 1967, Das traumatische apallische Syndrom. Springer Wien-New York
3. Gerstenbrand F., Lücking C.H., 1970. Die akuten traumatischen Hirnstammschäden. Arch Psychiat.
Nervenkr. 213, 264-281
4. Gerstenbrand F.,Rumpl E., 1995. Rehabilitation nach Hirnverletzung. Intensiv Med. / 832-845
5. Grcevic N., 1988. The concept of inner cerebral trauma, Scand J Rehab Med Suppl 17:25-31
6. Lindenberg R., Freytag E., 1960. The mechanism of cerebral contusions. Arch Path 69:440-469
7. Vos P.E. et al., 2002, Europ J Neurol., EFNS Guidelines on MTBI 9:207-219

THE SOCIETY FOR THE STUDY OF
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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.

Pharmacological neuroprotection

The strategy of neuroprotector treatment is to interfere with molecular cascades which determine neuronal dysfunction and death. Different etiological agents or biological events starting the same molecular cascades, and then neuronal death.

There are two main cell death patterns. In necrosis it is the cellular edema who leads to osmolysis, with the cell passively dying off. The released cell contents are a potent inflammatory stimulus.

Apoptosis, on the other hand, is an active process strictly genetically controlled which needs ATP and which often, but not always, leads to caspase activation. Usually there is no inflammation (stroke, trauma). The apoptosis-like processes differ from physiological apoptosis by a longer time span.

Anoikis is defined as apoptosis like that is induced by inadequate or inappropriate cellmatrix interactions.

In some cases all processes (necrosis, apoptosis, apoptosis like, anoikis) occurs at the same time.

Three major processes should be considered extremely important in the pathophysiology of TBI:

Excitotoxicity
Inflammation
Apoptosis like processes

Excitotoxicity

Intense insult such as occurring in the ischemic core after a stroke lead to neuronal cell swelling and lysis (necrosis) by massive stimulation of NMDA receptors.

More moderate NMDA receptor hyperactivity such as occurring of the ischemic penumbra of stroke, traumatic brain injury and in many slow-onset neurodegenerative diseases triggers free radicals formation and multiple pathways leading to apoptotic like damage.

Inflammation

The contribution of inflammation has been widely recognized in several neurological conditions such as multiple sclerosis (MS), Guillain-Barré syndrome (GBS), chronic inflammatory demyelinating neuropathy (CIDP), AIDS dementia, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, cerebral ischemia, traumatic brain injury.

However there are compelling evidences indicating that both inflammatory cells and mediators may also have beneficial functions assisting in repair and recovery processes.

The neuroprotective role of inflammation

Essential immunological functions such as B cell proliferation, immunoglobulin synthesis, antigen presentation by macrophages and expression of co-stimulatory molecules are influenced by NTFs.

Parallel between the strategies of traumatic brain injury treatment and strategies to acute stroke injury

Traumatic Brain injury	Stroke
Fast resuscitation after the injury	Prevention
Prompt evacuation of substantial mass lesion	Reperfusion
Adequate, adaptative intensive care	
Neuroprotection	Neuroprotection
Long term rehabilitation (for some)	Rehabilitation

The primary goal of neuroprotection in TBI is to prevent and reduce secondary damage and to enhance repair while the aim of neuroprotection in accute stroke is to prevent the death of neurons in the penumbra.

Neuroprotectants with relative mechanisms:

Calcium Channel Modulators
Sodium Channel Modulators
NMDA Receptor Antagonists
GABA Receptor Agonists
Antioxidants-Free Radical Scavengers
Adhesion Molecules
Adenosine Ago. & Antagonists

Neuroprotectants with absolute mechanisms:

Neurotrophic Factors
Neurotrophic Factors like molecules
Some classes of Cytokines

Brain trauma results in brain damage and dysfunction from both primary injury (due to biomechanical effects) and subsequent secondary injury due to activation of pathophysiologic cascades.

Secondary damage consists of many complex biochemical and cellular pathways that influence progression of the primary injury. In reality, brain damage develops sequentially (about one third of the patients who died after severe head injury have been awake and cooperative at some point after the impact), initiated neuroprotective treatment approaches aiming at the interruption of pathophysiological mechanisms leading to secondary brain injury.

Over the past decades our understanding of the pathophysiology of 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.

The new knowledge of the neurobiology and neuropharmacology of TBI should not divert our attention from the absolute importance of correcting hypoxia, hypotension, raised intracranial pressure and other causes of secondary ischemic insult.

Also we should not be discouraged by negative results and difficulties in previous clinical trials, but continue our search for effective neuroprotective drugs for TBI patients, better approaches and new clinical designs in order to further improve outcome.

Excitatory neurotransmitter antagonism

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.

Traxoprodil, a second-generation NMDA antagonist that selectively targets NMDA receptors containing the NR2B subunit, has been evaluated in a clinical trial.

The molecule was well tolerated and, although not statistically significant, resulted in increased favorable outcome and reduced mortality, which was more pronounced in the more severe subset of patients.

Dexanabinol is a synthetic cannabinoid without psychotropic activity, but strong neuroprotectant (due to antiexcitotoxic, antioxidant and anti-inflammatory properties). This drug was recently evaluated in a phase III trial and found safe, but not efficacious in the treatment of TBI. Efficacy of blocking excitotoxic responses following TBI as well as other insults to the central nervous system, to date, remains unproven.

Magnesium - One of the great advantages of magnesium, is its pleiotropic effect.

Despite all this evidence concerning the neuroprotective effects of magnesium, a recently completed randomized double-blind trial evaluating the efficacy of a 5-day continuous magnesium administration in 499 patients with moderate or severe TBI was unable to show neuroprotective effects.

Mitochondrial dysfunction

Mitochondrial dysfunction can be attenuated by inhibitors of mitochondrial permeability transition such as cyclosporin A and its derivatives.

Based on preclinical data cyclosporin A has been evaluated in two phase II clinical trials, and was found to improve cerebral perfusion pressure and cerebral metabolism, as evaluated with microdialysis. Cyclosporin A is considered safe in TBI patients, and its CSF pharmacokinetics in the injured central nervous system have been elucidated, supporting the initiative for a phase III clinical trial, which is currently being designed.
In experimental research, blockage of N-type voltage-gated calcium channels by ziconotide (SNX-111) has been shown to induce partial restoration of mitochondrial function, but a clinical trial was terminated prematurely because of increased mortality in the treatment group.

Erythropoietin

Erythropoietin has been shown to be neuroprotective in experimental models of stroke, and following experimental TBI.

A double-blind proof-of-concept trial showed no adverse events, and suggested improved functional outcome in erythropoietin- treated patients.
These results prompted a multicenter phase II/III trial in stroke patients, as well as an additional pharmacokinetic study evaluating CSF erythropoietin following systemic administration.

In TBI, a randomized phase II clinical trial is currently ongoing in Wisconsin, USA. This trial focuses primarily on moderate TBI patients, and instead of using the GlasgowOutcome Score evaluates neuronal cell-death markers as a primary outcome measure.

Hormones

A large meta-analysis suggests that no differences in outcome between men and women exist in outcome following TBI.

Both progesterone and allopregnanolone improve neuronal survival and functional recovery following experimental TBI.

A phase II clinical trial which concluded that no serious adverse events occurred due to progesterone administration in TBI patients. In moderate TBI survivors treated with progesterone, the outcome was better than in those treated with placebo.

Bradykinin antagonists

Specific inhibition of the B2-bradykinin receptor is considered a promising strategy for neuroprotection. A phase I clinical trial to investigate the pharmacokinetics of Anatibant, was conducted and published. Currently, a phase II safety study is being conducted on 500 patients with TBI.

Nitric oxide and inhibitors of nitric oxide synthases

Nitric oxide is a key factor in the development of secondary injury being potentially neurotoxic.

Clinical studies, however, failed to show benefit. A new drug currently under investigation is the compound VAS203, a structural analog of 5678-tetrahydro-l-biopterin (BH4), the endogenous cofactor of NOS, and one of the most potent inhibitors of NOSs discovered so far.

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.

Preclinical stage

In the preclinical stage, therapies are often tested on healthy, young animals under rigorously controlled laboratory conditions. The treatment is not adequately tested (for example, by multiple investigators in different TBI and stroke models) before it is brought to clinical trial.

Clinical Trial Stage

In this presentation we will highlight the comparison between stroke and TBI.
Comparison between the management of stroke and of traumatic brain injury:

Stroke type	TBI type
Stroke severity	TBI severity
Identifying the Ischemic Penumbra	
Time window for drug administration	Time window for drug administration
Combination therapy	Combination therapy
Dosing regimen	Dosing regimen
Statistical power	Statistical power
Study outcomes	Study outcomes

Bibliography

1. Marklund N, Bakshi A, Castelbuono DJ, et al. Evaluation of pharmacological treatment strategies in traumatic brain injury. Curr Pharm Des 2006; 12:16451680
2. Maas AI, Schouten JW, Teasdale GM. Neuroprotection. In: Reilly P, Bullock MR, editors. Head Injury. London: Hodder Arnold Publishers; 2005. pp. 406440.
3. Muir KW. Glutamate-based therapeutic approaches: clinical trials with NMDA antagonists. Curr Opin Pharm 2006; 6:5360
4. Willmore LJ. Antiepileptic drugs and neuroprotection: current status and future roles. Epilepsy Behav 2005; 7 (Suppl 3):S25S28.
5. Wang KK, Larner SF, Robinson G, Hayes RL. Neuroprotection targets after traumatic brain injury. Curr Opin Neurol 2006; 19:514519.
6. Chen HS, Lipton SA. The chemical biology of clinically tolerated NMDA receptor antagonists. J Neurochem 2006; 97:16111626.
7. Maas AI, Murray G, Henney H 3rd, et al. Efficacy and safety of dexanabinol in severe traumatic brain injury: results of a phase III randomised, placebocontrolled, clinical trial. Lancet Neurol 2006; 5:3845.
8. Temkin NR, Anderson GD, Winn HR, et al. Magnesium sulfate for neuroprotection after traumatic brain injury: a randomized controlled trial. Lancet Neurol 2007; 6:2938.
9. Muir KW, Lees KR, Ford I, et al. Magnesium for acute stroke (Intravenous Magnesium Efficacy in Stroke trial): randomised controlled trial. Lancet 2004;363:439445.
10. Mazzeo AT, Kunene NK, Gilman CB, et al. Severe human traumatic brain injury, but not cyclosporin A treatment, depresses activated T lymphocytes early after injury. J Neurotrauma 2006; 23:962975.
11. Hasselblatt M, Ehrenreich H, Siren AL. The brain erythropoietin system and its potential therapeutic exploitation in brain disease. J Neurosurg Anesth 2006; 18:132138.
12. Mushkudiani N, Engel DC, Steyerberg EW, et al. The prognostic value of demographic characteristics in traumatic brain injury: results from the IMPACT study. J Neurotrauma (in press).
13. Robertson CL, Puskar A, Hoffman GE, et al. Physiologic progesterone reduces mitochondrial dysfunction and hippocampal cell loss after traumatic brain injury in female rats. Exp Neurol 2006; 197:235243.
14. Wright DW, Kellermann AL, Hertzberg VS, et al. ProTECT: A randomized clinical trial of progesterone for acute traumatic brain injury. Ann Emerg Med 2006
15. Marmarou A, Guy M, Murphey L, et al. A single dose, three-arm, placebocontrolled, phase I study of the bradykinin B2 receptor antagonist Anatibant (LF16-0687Ms) in patients with severe traumatic brain injury. J Neurotrauma 2005; 22:14441455.
16. Marklund N, Bakshi A, Castelbuono DJ, et al. Evaluation of pharmacological treatment strategies in traumatic brain injury. Curr Pharm Des 2006; 12:1645 1680.
17. Doppenberg EM, Choi SC, Bullock R. Clinical trials in traumatic brain injury: lessons for the future. J Neurosurg Anesthesiol 2004; 16:8794.
18. Temkin NR, Anderson GD, Winn HR, et al. Magnesium sulfate for neuroprotection after traumatic brain injury: a randomized controlled trial. Lancet Neurol 2007; 6:2938.
19. Empey PE, McNamara PJ, Young B, et al. Cyclosporin A disposition following acute traumatic brain injury. J Neurotrauma 2006; 23:109116.
20. Wang KK, Larner SF, Robinson G, Hayes RL. Neuroprotection targets after traumatic brain injury. Curr Opin Neurol 2006; 19:514519.
21. Temkin NR, Anderson GD, Winn HR, et al. Magnesium sulfate for neuroprotection after traumatic brain injury: a randomized controlled trial. Lancet Neurol 2007; 6:2938.
22. Kevin K.W. Wanga, Stephen F. Larnera, Gillian Robinsonc and Ronald L. Hayesa, "Neuroprotection targets after traumatic brain injury"; Current Opinion in Neurology 2006, 19:514519

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BIOCHEMICAL MARKERS OF TRAUMATIC BRAIN INJURY

Abstract

Traumatic Brain Injury encompasses the functional disturbances and structural damage of the brain caused by direct impact, external acceleration, deceleration and/or rotation forces to the head. TBI may be a life threatening disease of predominantly young persons with a 30% case fatality rate in severe cases. Accurate determination of the initial severity of the primary brain damage after severe head injury is important to balance the risks and benefits of treatment(1) and in establishing neurologic prognosis.
This paper will review the value of determination of biomarker levels in peripheral blood after traumatic brain injury for neurologic prognosis. Especially the role of the brain specific proteins Glial Fibrillary Acidic Protein, S100β and Neuron Specific Enolase as indicators of injury severity will be discussed.

Introduction

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. 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.
Of all head injuries approximately 10% will be diagnosed with severe traumatic brain damage. Severe TBI is a life threatening disease of predominantly young persons with a 30% case fatality rate. Severe disabilities persist in over 50% of survivors. The young age at which severe TBI occurs and the 50% overall poor outcome explain why the loss of productive years is greater than that of subarachnoid haemorrhage and comparable to ischemic stroke.

Why study biomarkers of head injury?

Accurate determination of the initial severity of the primary brain damage after severe head injury is important to balance the risks and benefits of treatment(1) and in establishing neurologic prognosis. Outcome prediction remains difficult because neurological assessment is often influenced by the use of sedatives, analgetics and/or muscle relaxants.
Therefore biological markers that reliably reflect the extent of brain damage and are easy to measure (i.e. in peripheral blood) have long been searched for.(3) To study biomarkers of traumatic brain injury several options exist because after injury brain cells can deteriorate by more than one pathway, and many genes and proteins may be involved (4).
Previous studies have identified inflammatory response molecules, excitotoxic amino acids, oxidative stress markers and enzymes in cerebrospinal fluid (CSF).(3;5-9)
In recent years it has become clear that genetic factors may influence functional outcome of many diseases including TBI. The APOE-ε4 allele is associated with poor neurologic recovery after traumatic brain injury(10-12). A recent study however could not confirm the earlier findings and there was no overall association between APOE genotype and outcome although there was evidence of an interaction between age and APOE genotype on outcome(13). Nevertheless more and more polymorphisms in other genes are investigated for their influence on the recovery process after TBI(14).

Biomarkers that can be assessed in peripheral blood: the brain specific proteins

Measurement of CSF biomarkers requires placement of ventricular catheters, which may influence CSF protein levels.(15;16) Advances in the analysis of brain specific proteins, revealed elevated levels of serum S100β and neuron specific enolase (NSE) after stroke, traumatic brain injury, cardiopulmonary bypass surgery and cardiac arrest.(17-22)
S100β is a Ca2+-binding protein of astrocytes, oligodendrocytes and Schwann cells(23;24) and Neuron specific Enolase(NSE) is a cytoplasmic glycolytic enzyme of neurons.(25-27) Serum S100β and NSE levels correlate with contusion volume, presence of subarachnoid haemorrhage on CT and with clinical outcome after severe traumatic brain injury. (28-31)
Glial Fibrillary Acidic Protein (GFAP) is a monomeric intermediate filament protein of astrocytes. CSF concentrations of GFAP are elevated in normal pressure hydrocephalus, dementia and stroke.(32-34) In patients who died from traumatic brain injury increased immunoreactivity was present adjacent to cortical contusion zones.(35) GFAP can be measured in peripheral blood.(36;37) After stroke serum GFAP level correlates with infarct volume and neurological and functional status at discharge from the hospital.(20)

Brain-specific proteins, in particular S100β and neuron-specific enolase, may be released into the circulation after TBI. Serum levels of S100β are higher in patients with intracranial pathology and correlate with clinical outcome and the severity of primary and secondary brain damage(38;39). Undetectable or normal serum levels of S100β are predictive of normal intracranial findings on CT, and thus S100β could be used to select patients for CT after MTBI(38;40). These results have to be confirmed in large prospective studies. Although this finding has already been questioned: normal serum S100β levels may be present after epidural haematoma (Unden, 2005 3250 /id). In the future, this may be of relevance in the medicallegal context to prove that the acute symptoms and signs and/or the long-term disability or neuropsychological impairments after MTBI are indeed a consequence of structural brain damage or of psychological stress in reaction to the event, alcohol intoxication, pre-existent disorders, systemic injury, or other causes.

Biomarkers of injury severity or with predictive ability for outcome in traumatic brain injury

Biomarker/Type	Biomarker	Location	Compartment	Reference
Neuronal Intracellular	NSE	Cytoplasm of neurons platelets,blood cells	CSF/Blood	(25-27)
Myelin	MBP	Myelin protein	CSF	(42)
Axonal	Tau	Micro tubule associated	CSF/Blood	(43)
	SBDP	Axonal skeleton	CSF/Blood	(44)
Glial	S100β	Astroglial bone marrow subcutaneous fat skeletal muscle	CSF/Blood	(23;24)
	GFAP	Astroglial skeleton	CSF/Blood	(37)

Table. Abbreviations: NSE=Neuron Specific Enolase;MBP=Myelin Basic Proetin;SBDP=Spectrin breakdown products;GFAP=Glia Fibrillary Acidic Protein

Pathophysiology of brain specific proteins

As mentioned before the use of peripheral blood for the determination of brain damage biomarker levels is probably advantageous beause it is easier to obtain and does not bear the risk of infection of the central nervous system. Compared to CSF, over time the S100β wash-out patterns are similar although peak levels are delayed(45).

Brain specific proteins may enter the circulation via various routes and it seems that serum S100β, GFAP and to a lesser extent NSE levels differ according to location and type of the damage with higher levels if intraparenchymal damage is present or in the presence of intraventricular blood as compared to the location of blood in the subarachnoidal space(46). Several explanations exist 1: Iron, which is contained within haemoglobin, causes a reactive astrocytosis with the release of S100β and GFAP(45).

2: Presence of intracerebral blood leads to increased astrocytosis compared to the presence of blood limited to the subarachnoid space only. Upon brain tissue damage (neuronal and) glial proteins are released from brain cells and subsequently appear in the systemic circulation, either directly via passage through the disturbed blood-brain barrier or indirectly via release into the CSF followed by absorption through the intraventricular choroid plexus or via arachnoid villi into the cerebral sinuses. Simultaneous transport of S100β, GFAP (and NSE) via both the direct and the indirect pathways results in higher serum concentrations than transport through the indirect pathway alone. Several other factors may also affect protein CSF and serum levels: the distance between the affected brain and the CSF compartment, the severity and extent of the damage, degradation of proteins by proteinases either locally or in the CSF(47). The role of medication on protein serum levels is unknown but acute alcohol intoxication does not influence measurements of S-100β and NSE in patients with mild head injury(48;49).

NSE is mainly found in neurons, while S100β and GFAP are found in astroglial cells. S100β is a functional protein located in the cytoplasm, GFAP is a structural protein of the cytoskeleton. Since the brain specific proteins are derived from different cell types with different molecular weights (S100β=21 kDa, GFAP=50 kDa, NSE=90 kDa) which may affect the dynamics of release and transport over specific barriers, the timing of sample acquisition is also important(47). Indeed serial sampling has revealed different release patterns of S100β and GFAP after ischemic stroke(20). A recent study showed a non-significant increase in serum S100β level on day 2 compared to day 1 after SAH(45). A short lasting release of S-100β in serum was found in soccer players 60-360 minutes after repetitive heading(50). The time to sample withdrawal varied extensively in our patient group between 0.5 and 56 hours, partly due to the fact that some patients were secondary referrals.

(1) Signorini DF, Andrews PJ, Jones PA, Wardlaw JM, Miller JD. Predicting survival using simple clinical variables: a case study in traumatic brain injury. J Neurol Neurosurg Psychiatry 1999;66:20-5.

(2) Meerhoff SR, de Kruijk JR, Rutten J, Leffers P, Twijnstra A. De incidentie van traumatisch schedel- of hersenletsel in het adherentie gebied van het Academisch Ziekenhuis Maastricht in 1997. Ned Tijdschr Geneeskd 2000 Sep 30;144(40):1915-8.

(3) Bakay RA, Sweeney KM, Wood JH. Pathophysiology of cerebrospinal fluid in head injury: Part 2. Biochemical markers for central nervous system trauma. Neurosurgery 1986 Mar;18(3):376-82.

(4) Pineda JA, Wang KK, Hayes RL. Biomarkers of proteolytic damage following traumatic brain injury. Brain Pathol 2004 Apr;14(2):202-9.

(5) Hans P, Born JD, Chapelle JP, Milbouw G. Creatine kinase isoenzymes in severe head injury. J Neurosurg 1983 May;58(5):689-92.

(6) Kossmann T, Stahel PF, Lenzlinger PM, Redl H, Dubs RW, Trentz O, et al. Interleukin-8 released into the cerebrospinal fluid after brain injury is associated with blood-brain barrier dysfunction and nerve growth factor production. J Cereb Blood Flow Metab 1997 Mar;17(3):280-9.

(7) Bell MJ, Kochanek PM, Heyes MP, Wisniewski SR, Sinz EH, Clark RS, et al. Quinolinic acid in the cerebrospinal fluid of children after traumatic brain injury. Crit Care Med 1999 Mar;27(3):493-7.

(8) Hans P, Born JD, Albert A. "Extrapolated" creatine kinase-BB isoenzyme activity in assessment of initial brain damage after severe head injury. J Neurosurg 1987 May;66(5):714-7.

(9) Morganti-Kossmann MC, Hans VH, Lenzlinger PM, Dubs R, Ludwig E, Trentz O, et al. TGF-beta is elevated in the CSF of patients with severe traumatic brain injuries and parallels blood-brain barrier function. J Neurotrauma 1999 Jul;16(7):617-28.

(10) Teasdale GM, Nicoll JA, Murray G, Fiddes M. Association of apolipoprotein E polymorphism with outcome after head injury. Lancet 1997 Oct 11;350(9084):1069-71.

(11) Sorbi S, Nacmias B, Piacentini S, Repice A, Latorraca S, Forleo P, et al. ApoE as a prognostic factor for post-traumatic coma. Nat Med 1995 Sep;1(9):852.

(12) Friedman G, Froom P, Sazbon L, Grinblatt I, Shochina M, Tsenter J, et al. Apolipoprotein E-epsilon4 genotype predicts a poor outcome in survivors of traumatic brain injury. Neurology 1999 Jan 15;52(2):244-8.

(13) Teasdale GM, Murray GD, Nicoll JA. The association between APOE epsilon4, age and outcome after head injury: a prospective cohort study. Brain 2005 Nov;128(Pt 11):2556-61.

(14) Waters RJ, Nicoll JA. Genetic influences on outcome following acute neurological insults. Curr Opin Crit Care 2005 Apr;11(2):105-10.

(15) Berger RP, Pierce MC, Wisniewski SR, Adelson PD, Clark RS, Ruppel RA, et al. Neuron-specific enolase and S100B in cerebrospinal fluid after severe traumatic brain injury in infants and children. Pediatrics 2002 Feb;109(2):E31.

(16) Kruse A, Cesarini KG, Bach FW, Persson L. Increases of neuron-specific enolase, S-100 protein, creatine kinase and creatine kinase BB isoenzyme in CSF following intraventricular catheter implantation. Acta Neurochir 1991;110(3-4):106-9.

(17) Persson L, Hardemark HG, Gustafsson J, Rundstrom G, Mendel Hartvig I, Esscher T, et al. S-100 protein and neuron-specific enolase in cerebrospinal fluid and serum: markers of cell damage in human central nervous system. Stroke 1987;18(5):911-8.

(18) Raabe A, Grolms C, Seifert V. Serum markers of brain damage and outcome prediction in patients after severe head injury. Br J Neurosurg 1999 Feb;13(1):56-9.

(19) Rosen H, Rosengren L, Herlitz J, Blomstrand C. Increased serum levels of the S-100 protein are associated with hypoxic brain damage after cardiac arrest. Stroke 1998;29(2):473-7.

(20) Herrmann M, Vos PE, Wunderlich MT, de Bruijn CH, Lamers KJB. Release of glial tissue-specific proteins after acute stroke : A comparative analysis of serum concentrations of protein S-100B and glial fibrillary acidic protein. Stroke 2000 Nov;31(11):2670-7.

(21) Missler U, Wiesmann M, Friedrich C, Kaps M. S-100 protein and neuron-specific enolase concentrations in blood as indicators of infarction volume and prognosis in acute ischemic stroke. Stroke 1997 Oct;28(10):1956-60.

(22) Anderson RE, Hansson LO, Vaage J. Release of S100B during coronary artery bypass grafting is reduced by off-pump surgery. Ann Thorac Surg 1999 Jun;67(6):1721-5.

(23) Schafer BW, Heizmann CW. The S100 family of EF-hand calcium-binding proteins: functions and pathology. Trends Biochem Sci 1996 Apr;21(4):134-40.

(24) Zimmer DB, Cornwall EH, Landar A, Song W. The S100 protein family: history, function, and expression. Brain Res Bull 1995;37(4):417-29.

(25) Schmitt B, Bauersfeld U, Schmid ER, Tuchschmid P, Molinari L, Fanconi S, et al. Serum and CSF levels of neuron-specific enolase (NSE) in cardiac surgery with cardiopulmonary bypass: a marker of brain injury? Brain Dev 1998 Oct;20(7):536-9.

(26) Gerbitz KD, Summer J, Schumacher I, Arnold H, Kraft A, Mross K. Enolase isoenzymes as tumour markers. J Clin Chem Clin Biochem 1986 Dec;24(12):1009-16.

(27) Marangos PJ, Schmechel DE. Neuron specific enolase, a clinically useful marker for neurons and neuroendocrine cells. Annu Rev Neurosci 1987;10:269-95.

(28) Raabe A, Grolms C, Sorge O, Zimmermann M, Seifert V. Serum S-100B protein in severe head injury. Neurosurgery 1999 Sep;45(3):477-83.

(29) Raabe A, Grolms C, Keller M, Dohnert J, Sorge O, Seifert V. Correlation of computed tomography findings and serum brain damage markers following severe head injury. Acta Neurochir 1998;140(8):787-91.

(30) Woertgen C, Rothoerl RD, Holzschuh M, Metz C, Brawanski A. Comparison of serial S-100 and NSE serum measurements after severe head injury. Acta Neurochir 1997;139(12):1161-4.

(31) Yamazaki Y, Yada K, Morii S, Kitahara T, Ohwada T. Diagnostic significance of serum neuron-specific enolase and myelin basic protein assay in patients with acute head injury. Surg Neurol 1995;43(3):267-70.

(32) Aurell A, Rosengren LE, Karlsson B, Olsson JE, Zbornikova V, Haglid KG. Determination of S-100 and glial fibrillary acidic protein concentrations in cerebrospinal fluid after brain infarction. Stroke 1991 Oct;22(10):1254-8.

(33) Tullberg M, Rosengren L, Blomsterwall E, Karlsson JE, Wikkelso C, gfap. CSF neurofilament and glial fibrillary acidic protein in normal pressure hydrocephalus. Neurology 1998 Apr;50(4):1122-7.

(34) Wallin A, Blennow K, Rosengren LE. Glial fibrillary acidic protein in the cerebrospinal fluid of patients with dementia. Dementia 1996 Sep;7(5):267-72.

(35) Hausmann R, Riess R, Fieguth A, Betz P. Immunohistochemical investigations on the course of astroglial GFAP expression following human brain injury. Int J Legal Med 2000 ;113 (2):70 -5113(2):70-5.

(36) Missler U, Wiesmann M, Wittmann G, Magerkurth O, Hagenstrom H. Measurement of glial fibrillary acidic protein in human blood: analytical method and preliminary clinical results. Clin Chem 1999 Jan;45(1):138-41.

(37) van Geel WJA, de Reus HPM, Nijzing H, Verbeek MM, Vos PE, Lamers KJB. Measurement of glial fibrillary acidic protein in blood: an analytical method. Clin Chim Acta 2002 Dec;326(1-2):151-4.

(38) Romner B, Ingebrigtsen T, Kongstad P, Borgesen SE. Traumatic brain damage: serum S-100 protein measurements related to neuroradiological findings. J Neurotrauma 2000 Aug;17(8):641-7.

(39) 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.

(40) Biberthaler P, Mussack T, Kanz KG, Linsenmaier U, Pfeifer KJ, Mutschler W, et al. Identification of high-risk patients after minor craniocerebral trauma. Measurement of nerve tissue protein S 100. Unfallchirurg 2004 Mar;107(3):197-202.

(41) Unden J, Bellner J, Astrand R, Romner B. Serum S100B levels in patients with epidural haematomas. Br J Neurosurg 2005 Feb;19(1):43-5.

(42) Lamers KJB, Van Engelen BG, Gabreels FJ, Hommes OR, Borm GF, Wevers RA. Cerebrospinal neuron-specific enolase, S-100 and myelin basic protein in neurological disorders. Acta Neurol Scand 1995 Sep;92(3):247-51.

(43) Shaw GJ, Jauch EC, Zemlan FP. Serum cleaved tau protein levels and clinical outcome in adult patients with closed head injury. Ann Emerg Med 2002 Mar;39(3):254-7.

(44) Farkas O, Polgar B, Szekeres-Bartho J, Doczi T, Povlishock JT, Buki A. Spectrin breakdown products in the cerebrospinal fluid in severe head injury--preliminary observations. Acta Neurochir (Wien) 2005 Aug;147(8):855-61.

(45) Petzold A, Keir G, Lim D, Smith M, Thompson EJ. Cerebrospinal fluid (CSF) and serum S100B: release and wash-out pattern. Brain Res Bull 2003 Aug 15;61(3):281-5.

(46) Vos PE, van GM, Beems T, Zimmerman C, Verbeek MM. Increased GFAP and S100beta but not NSE serum levels after subarachnoid haemorrhage are associated with clinical severity. Eur J Neurol 2006 Jun;13(6):632-8.

(47) Lamers KJ, Vos PE, Verbeek MM, Rosmalen F, van Geel WJ, Van Engelen BG. Protein S-100B, neuron-specific enolase (NSE), myelin basic protein (MBP) and glial fibrillary acidic protein (GFAP) in cerebrospinal fluid (CSF) and blood of neurological patients. Brain Res Bull 2003 Aug 15;61(3):261-4.

(48) Biberthaler P, Mussack T, Wiedemann E, Gilg T, Soyka M, Koller G, et al. Elevated serum levels of S-100B reflect the extent of brain injury in alcohol intoxicated patients after mild

head trauma. Shock 2001 Aug;16(2):97-101.

(49) Mussack T, Biberthaler P, Kanz KG, Heckl U, Gruber R, Linsenmaier U, et al. Immediate S-100B and neuron-specific enolase plasma measurements for rapid evaluation of primary brain damage in alcohol-intoxicated, minor head-injured patients. Shock 2002 Nov;18(5):395-400.

(50) Mussack T, Dvoruk J, Graf-Baumann T, Jochum M. Serum S-100B protein levels in young amateur soccer players after controlled heading and normal exercise. Eur J Med Res 2003 Oct 22;8(10):457-64.

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PREDICTION OF OUTCOME IN TRAUMATIC BRAIN INJURY

Lessons from the German prospective study on 6800 acute TBI and the German Coma Remission Scale Score (CRS) for assessment of impaired higher cortical functioning, quality management, and outcome.

Abstract

Objective: Increasingly more patients survive after acute brain damage, in many cases, however, suffering from severe impairments and disability(1). The German Coma Remission Scale (CRS) aims at the assessment of restoration of impaired higher cortical functioning (2)

Methods: First prospective population based study on quality management of 6.783 acute TBI in Germany in the years 2000/2001 (3). Impairments refer to loss of structures and functions. Disabilities refer to limitations or participating restrictions. Functioning is an umbrella term encompassing all body functions, activities and social participation (WHO-ICF 2001). Nowadays the GCS (Glasgow Coma Scale, Teasdale and Jennett,1974)and the GOS (Glasgow Outcome Scale, Jennett and Bond,1975) are widely used in clinical practice, notwithstanding that " permanent" for vegetative state ("P"VS) is not used any more (Jennett, 2002). Minimally conscious state (MCS, Giacgino et al 1997) is now accepted as the diagnose for minimally responsive patients who regained consciousness = early functional recovery state when emerging from coma and/or Apallic Syndrome to a certain extent , but who are otherwise unable to initiate purposeful behaviour or communicate intelligibly (4).

Results: 91% of 6.783 acute TBI were diagnosed as mild (MTBI),4% moderate, 5% severe.

76.5% of all TBI were admitted for in-patient hospital treatment. Only 258 pts out of tem (3,8%) were afterwards admitted to an rehabilitation institute,67,8% with GCS and CRS scores.Early neurological-neurosurgical neurorehabilitation (ENNR) aims at restoration of impaired functioning after brain damage. The German CRS (1,2) has been introduced 1993 for the assessment of recovery of higher cortical functioning from coma and AS/VS by adding up the GCS with aid of nine additional items for

Neurobehavioral functions (arousability/ attention, motor and sensible responses): 1.Aurousability/attention (max.5 pts); 2.motoric response (max 6);3. response to acoustic stimuli (max 3); 4.response to visual stimuli (max 4); 5. response to tactile stimuli (max 3); 6. response to speech-motor (logomotor) response (max 6 pts) Maximal score 24 points (cut off point for ENNR= >40 Early Rehab. Barthel Index). The best sum score reflects best functional performance at a given time .Analysis of GOS of 270 EENR patients 2 ½ years (median) following TBI showed that no patient with less than 20 points CRS on day 40 achieved a final GOS of 4 or 5 , all patients CRS less than 10 remained GOS 2 or 1;all patients CRS 24 at day 40 recovered to GOS 4 or 5. One-year-outcome (telephone interview) of N=4.307 TBI =63,5%:
revealed complete social reintegration in 94% of them(went back to school/work);45% were still under medical treatment. 1% had died, 64% within the first 24 hours. 2 pts were apallic.

Discussion: GSC was assessed in only 57% of TBI. Less than 4% of in patients received neurorehabilitation. CRS is an efficient, reliable, prognostic measuring tool that can easily be used by all ENNR team members. Disability is reflected by neuropsychological impairments.

Take home message: GCS is mandatory in TBI. CRS at day 40 ENNR has a prognostic potency for impaired higher cortical functioning. MTBI might cause severe brain damage. Disability is a difficulty in functioning at the body, person, or social level, in one or more life domaines, as experienced by an individual with a health condition in interaction with contextual factors(5).

References

1. Ortega-Stuhrsamp E., von Wild KRH (2001) in Acta Neurochir (Suppl) 79, 11-14
2. Von Wild KRH (2000) in Schmidek HH (ed) Operative neurosurgical techniques pp 45-60
3. von Wild KRH et al(2005)Neurorehabilitation following Craniocerebral Trauma European J Trauma4,24-58
4.Zasler N, Katz D, Zafonte RD (2007)Brain Injury Medicine, Demos, New York
5.Leonardi M et al (2006) The definition of disability: what is in a name www.thelancet.com Vol6 Oct 7,1219-21