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Overview

Update on biological, social and economical aspect of Alzheimer's diasease and other dementia*

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DEMENTIA SYNDROME: DEFINITION, CLASSIFICATION, EPIDEMIOLOGY

Dementia is tipycally late-onset clinical condition with most cases developing in people aged 65 and more. It is characterized by a progressive decline in memory and other cognitive abilities, including at least one of the following:

- an ability to generate coherent speech or understand spoken or written language
- an ability to recognize or identify objects
- an ability to execute motor activities, assuming intact motor function
- an ability to think abstractly, make sound judgments and plans and perform complex tasks.

Alzheimer's disease is the most common cause of dementia, accounting for approximately 2/3 of all cases of dementia. The rest includes, in almost equal proportions, vascular dementia and other types of dementia (Table 1). Although different types of dementia can be distinguished according to specific symptom patterns and microscopic brain abnormalities (on autopsy), there is a large range of overlap between them. This can further be complicated by coexisting medical conditions, such as depression and disorders of vascular origin, frequently occurring in people at advanced age. So, pure forms of dementia rarely exist and most cases reflect mixed underlying clinical conditions, but all result in progressive damaging of brain cells and more or less unique pathologic features.

It is estimated that dementia affects more than 35 million people worldwide. This figure is predicted to be tripled in the forthcoming decades due to the aging of population. This will increase the financial burden for healthcare systems and communities, because dementia syndrome is, in its severe stage, characterized by progressive loss of functional independence. A need for increasing levels of supervision and personal care and possibly for nursing home placement, and ultimately, death in 4–10 years after the diagnosis is the natural course of a dementia syndrome (Figure 1). Whereas other major causes of death, such as heart disease, stroke, breast cancer and prostate cancer, are on

*update based on International conference on Alzheimer's disease and other dementia held in Vienna, July 2009.

TABLE 1

Common types of dementia and their typical characteristics

(source: Alzheimer's Association / Alzheimer's & Dementia 5 (2009) 234-270)

Type of dementia	Characteristics
Alzheimer's disease	Most common type of dementia, accounting for 60%-80% of cases
	Clinical course: steady and progressive loss of memory and cognitive faculties, including language, visuospatial skills and judgement
	Early symptoms: difficulties in remembering names and recent events, apathy and depression
	Later symptoms: impaired judgment, disorientation, confusion, behavior changes, trouble in speaking, swallowing and walking
	Neuropathology: extracellular Aβ-amyloid deposits (senile plaques) and intracellular strands composed of tau-proteins (tangles)
	Radiographic features: temporal and hippocampal cortex atrophy
Vascular cognitive impairment / Vascular dementia	The second most common type of dementia, also known as multi-infarct or post-stroke dementia
	Clinical course: highly variable and fluctuating, a stepwise decline of cognitive faculties, relatively perserved memory
	Radiographic features: evidence of an ischemic lesion, white matter damage, microinfarction
Mixed dementia	Characterized by the presence of the hallmark abnormalities of Alzheimer's and another type of dementia, most commonly vascular dementia, but also other types, such as dementia with Lewy bodies
Dementia with Lewy bodies	**Clinical characteristics:** similar to Alzheimer's disease, including problems with memory and judgment and behavior changes, cognitive symptoms may fluctuate daily
	Visual hallucinations, muscle rigidity and tremor are common
	Neuropathology: Lewy bodies (abmormal deposits of the protein α-synuclein, inside nerve cells)
Parkinson's dementia	Many patients with Parkinson's disease develop dementia in the later stages of the disease
	Neuropathology: hallmark Lewy bodies
Frontotemporal dementia	Typical localization in the front and side regions of the brain (one type is Pick's disease)
	Clinical symptoms: changes in personality and behavior and difficulties with language
Creutzfeldt-Jakob disease	Rapidly fatal disorder
	Clinical symptoms: impaired memory, coordination, behavior changes
	Variants are caused by consumption of products from cattle affected by mad cow disease, caused by the misfolding of prion protein throughout the brain
Normal pressure hydrocephalus	Caused by the retention of fluid in the brain
	Can sometimes be corrected with surgicall installation of a shunt in the brain to drain excess fluid
	Clinical symtoms: difficulties in walking, impaired memory, inability to control urine

the decrease, death attributed to Alzheimer's disease increases dramatically (47% increase between 2000 and 2006). This is why Alzheimer's disease and other dementia today represent one of the most urgent medical, social and economic challenges.

ELUCIDATING THE PATHOPHYSIOLOGY OF ALZHEIMER'S DISEASE IS THE BASIS FOR DEVELOPING DISEASE MODIFYING TREATMENTS

Alois Alzheimer gave the first description of Alzheimer's dementia in the early 1900s. Almost a century has gone without considerable advances with respect to treatment of this disorder. Available medications produce only temporary relief of symptoms, but are not able to stop disease progression (Table 2). In the last two decades, an important step has been made in understanding molecular cascades underlying the neuropathology of Alzheimer's disease (AD). These advances have provided the framework for the recent breakthrough in new therapeutic strategies that are believed to have a potential to change the course of the disease (Table 2).

AD is neuropathologically characterized by the deposition of senile plaques and neurofibrillary tangles and neuronal cell degeneration and loss. Two main hypotheses try to explain the pathogenesis of AD: the *cholinergic hypothesis* and the *Aβ-cascade hypothesis*. The majority of drugs, currently licensed or still under the investigation, have been manufactured according to these hypotheses (Table 2).

The *cholinergic hypothesis* states that selective loss of cholinergic function (associated with the action of the neurotransmitter acetylcholine) in the brain is the cause of cognitive decline in AD. This has been supported by a

TABLE 2

Alzheimer's disease medications approved for use by the US Food and Drug Administration (FDA) or currently in phase II or phase III clinical trials.

Symptomatic drugs, cholinesterase inhibitors, **Approved for use by the US FDA,**
Donezepil (Aricept), 1997.
Rivastigmine (Exelon), 2000.
Galantamine (Reminyl), 2001.
Tacrine (Cognex), 2003.
Memantine (Namenda, Axura, Ebixa, Memox), 2003
In phase II and phase III clinical trials
The first antiamyloid drugs, failed in phase III
Tramiprosate – Aβ-binding compound, amyloid aggregation inhibitor
Tarenflurbil – modulator of the γ-secretase activity, reducing generation of Aβ amyloid peptides
Currently in clinical trials
Bapineuzumab – monoclonal amino terminus-specific anti-amyloid antibody
Rember (methylene blue) – the first anti-tangle medication
Dimebon – neuroprotection, inhibition of the brain cell death
(multiple mechanisms of action: blocking the action of Aβ amyloid peptides and calcium-channels, modulating the activity of AMPA and NMDA glutamate receptors, blocking mitochondrial pores and modulating a number of other receptors)
Flurizan – a selective $A\beta_{42}$-lowering agent
LY450139 – a γ-secretase inhibitor
AN1792 – a vaccine
Cerebrolysin – neurotrophic factor (similar to Nerve Growth Factor), acts as signal molecule with pleiotropic effects at the cellular level, including: neuroprotection, neurogenesis and neuroplasticity

number of experiments indicating reduced synthesis, impaired transport and disrupted receptor signaling of acetylcholine, accompanied with selective loss of cholinergic neurons and reduced density of acetylcholine receptors. Currently approved symptomatic drugs for the treatment of AD are acetylcholinesterase-inhibitors which act in this way to slowdown the breakdown of the neurotransmitter acetylcholine, thereby prolonging its life and increasing its amount in the brain.

The *Aβ cascade hypothesis* advocates the statement that senile plaques and other neurodegenerative changes in Alzheimer's disease develop as the result of the accumulation of β-Amyloid (Aβ) peptides in the brain (Figure 2).

Aβ peptides are fragments, 39-43 amino acid residues in length, generated by cleavage from the Amyloid Precursor Protein (APP) – normal component of cellular membrane (Figure 2). Two enzymes, β-secretase and γ-secretase, have been identified as essential for the generation of these fragments, important because of their ability to aggregate. Only a small amount of APP is normally processed in this manner, while APP is predominantly processed by α-secretase, producing non-amyloidogenic APP α fragments (Figure 2).

Aβ peptides, particularly Aβ42, assembly into fibrillar aggregates on the basis of their conformational changes. Their accumulation in the brain is an early event during the course of AD, preceding the neurofibrillary tangles formation and the appearance of clinical symptoms. This is the consequence of either their enhanced production or/and diminished clearance. Exact knowledge about mechanisms involved in the amyloidogenic pathway has important implications for identification of target points for therapeutic research.

The Aβ hypothesis has lost on popularity upon observations that Aβ deposits poorly correlate with neuronal cell death and the severity of clinical symptoms. However, recent findings strongly argue in favor of the amyloidogenic hypothesis and its potential to provide an explanation of the mechanisms of neurodegeneration. These new findings include the identification of soluble, diffusible oligomeric forms of Aβ peptides, found to be highly neurotoxic. This opens a new avenue for treatment research – that aimed at searching for inhibitors of receptors which mediate Aβ trafficking and toxicity.

Neurofibrillary tangles, another neuropathological hallmark of AD, are likely to be more relevant than Aβ peptides in mediating neuronal cell death. Therefore, interruption of cascades involved in tangle formation is likely to be more promising as a disease modifying treatment.

Tangles are intracellularry accumulated aberrantly folded, tau proteins. In physiologic conditions, tau is a soluble protein that normally promotes microtubular stability. Normal microtubule function is essential for axonal integrity and connectivity and, finally, for providing the plasticity of synapses.

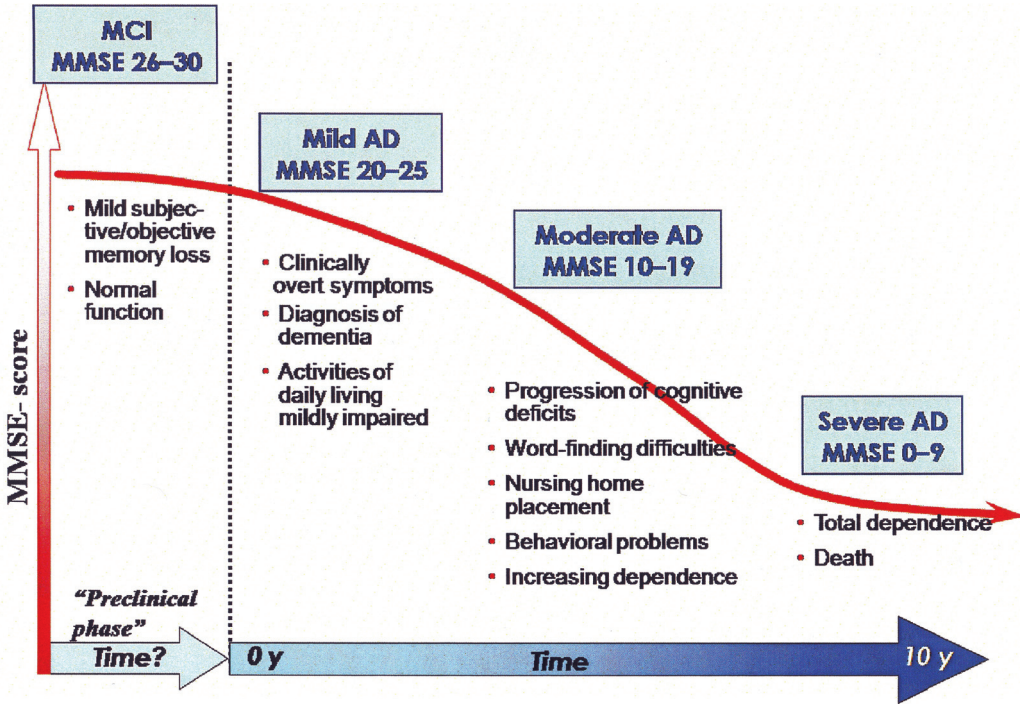

Figure 1. *The spectrum of therapeutics for Alzheimer's disease. (source: promoting materials)*

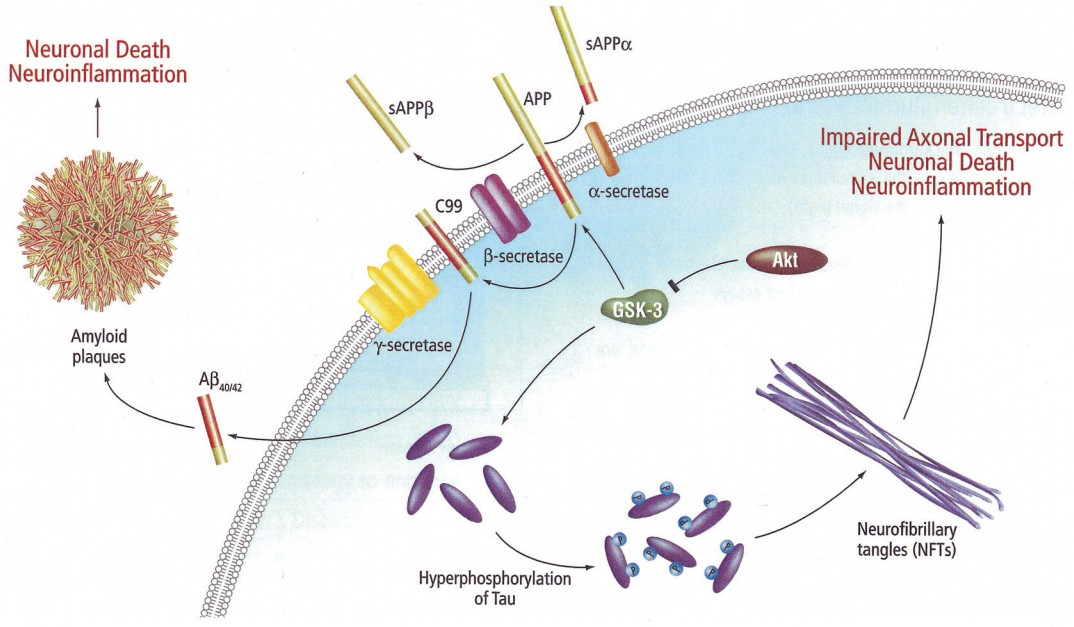

Figure 2. *Senile plaques, composed of aggregated Aβ amyloid proteins, and neurofibrillary tangles (misfolded tau proteins), are the neuropathological hallmarks of Alzheimer's disease. (source: promoting materials)*

Posttranslational modifications of tau by mechanisms such as hyperphosphorylation (due to high levels of serine and threonine residues) lead to conformational changes of a native protein. In this way, tau becomes resistant to degradation, loses its physiological functions and gains toxic abilities, actively promoting neuroinflammation and neuronal cell death (Figure 2).

According to these findings, the main targets for therapeutic interventions may be affected through the inhibition of the activity of protein kinases - enzymes included in phosphorylation of tau. Another approach is microtubule stabilizing drugs. Efforts are also focused on modulating the intracellular ubiqutin system responsible for refolding of aberrantly folded proteins.

One of the most promising strategy for the treatment of AD, currently under evaluation in clinical trials, is immunotherapy. Either by passive immunotherapy (monoclonal antibodies recognizing particular epitopes on Aβ or phosphorylated tau molecules, administered intravenously), or by active immunotherapy (vaccines containing Aβ or phospho-tau derivatives in combination with strong adjuvants, capable to induce specific antibody response) – the mechanism of action is the same – selective clearance of pathological neuroproteins from the brain, followed by the improvements in clinical symptoms.

Upon binding Aβ or phospho-tau fragments in the blood, specific antibodies (administered passively or actively produced in the body) initiate their clearance, using one of the following mechanisms: stimulated phagocytosis, ubiquitin independent intracellular degradation via lysosomes, or ubiqutin dependent intracellular degradation. This is followed by the removal of pathological aggregates from the brain to balance the blood levels of neuropeptides.

Alternatively, either passively administered, or actively produced in the peripheral immune system, specific antibodies can enter the CNS directly, passing the blood-brain barrier by actually both, receptor-mediated transport and passive diffusion. This is likely to be the predominant way of immune-mediated neuropeptide clearance. Actually, in a disease state, especially in AD, the permeability of the blood-brain barrier is increased, allowing specific antibodies to pass by.

As a curiosity of an immune-based therapy, antibodies with chaperon-like activities have recently been manufactured. These antibodies, by binding to specific sites on misfolded tau molecules, are capable to reverse their conformation in forms more prone for degradation via ubiquitin dependent pathway.

Aβ and tau pathologic pathways have been shown to interact with each other in a synergistic way. It is suggested, therefore, that reaching both by therapy should be more effective. This may be achieved by employing multiple targets treatments, or by the treatment focused on a single molecular target, but sharing multiple pathogenetic pathways.

The enzyme glycogen synthase kinase-3 (GSK-3), identified long time ago as an actor in the insulin signaling pathway, is one of such promising single-molecular targets for the treatment of AD, capable to exert multiple therapeutic effects. It has been shown that increased activity of this enzyme is associated with both tau hyperphosphorylation and increased Aβ peptide generation. Based on these findings, intense research of GSK-3 inhibitors is now underway.

Many other molecular pathways underlying neurodegenerative processes are currently under investigation, suggesting novel therapeutic approaches. For example, the *Metals Hypothesis* states that altered metabolism of endogenous brain metals, such as zinc, copper, or calcium, is involved in neurodegenerative processes. Based on this hypothesis, metal chelators are new candidate drugs for the treatment of AD.

Furthermore, it is well known that hypertension and atherosclerotic vascular disease reduce brain perfusion and may precipitate chronic ischemic conditions associated with cognitive impairments. Although a distinct difference exists between vascular type of dementia and AD regarding clinical symptoms and neuropathologic changes, a large body of evidence suggests that convergent processes are included in the progression of both cardiovascular and neurodegenerative diseases. Actually, the same risk factors and dysregulated molecular mechanisms, such as oxidative stress, hyperhomocysteinemia, inflammation, reduced glucose metabolism and mitochondrial abnormalities, already confirmed to be included in cardiovascular pathology, are likely to have a potential to initiate and/or strengthen the progression of neurodegenerative processes.

Related to this, many clinical studies are currently being conducted with the aim to evaluate the effects of antioxidative drugs (e.g. vitamins C and E, selegiline, α-tocopherol and plant flavonoids), antiinflammatory drugs (e.g. naproxen, rofecoxib, Ginkgo biloba extract), B-vitamin supplementation (to cure hyperhomocysteinemia) and some specific agents interfering with increased oxidative stress and impaired glucose metabolism, such as inhibitors of receptors for advanced glycation end products (RAGE).

There is some evidence that classical cardiovascular drugs, including statins and drugs affecting the renin angiotensin system, can also elicit positive therapeutic effects on the course of AD.

Long-standing paradigm that neurons do not regenerate during adulthood does not hold any more, as neuronal stem cells have been isolated from adult brain. New technologies are currently under investigation to allow using stem cells in neuroplacement therapy.

Nerve growth factor has received an attention as a potential therapeutic agent for AD due to its selective neurotropic activities on the brain cholinergic system. The main obstacles for its clinical use are the need for its direct neurosurgical delivery to the brain and considerable toxic side-effects. It is believed that this might be overcome by using small molecule approach (neurotrophins). This approach is based on using simple chemical compounds which are able to pass the blood-brain barrier upon systemic administration and to activate the Nerve Growth Factor signaling pathway at specific sites.

Only five drugs are currently approved by the American Food and Drug Administration (FDA) for the treatment of AD (Table 2).

In contrast, over a hundred disease modifying treatments are under clinical evaluation (Table 2). Disease modifying therapeutics are expected to slow disease progression rate by at least 25%–30%, to interfere with pathophysiologic mechanisms and to show a long-lasting (at least 18 months) beneficial effects on clinical symptoms.

However, many clinical trials have failed to show clear clinical benefits, or have been halted because of adverse effects. Groups of experts consider the methodological issues to find reasonable explanation for such results. Discussion is focused on study design, outcome measures, the use of biomarkers in monitoring disease progression and an appropriate target population selection. Special attention is paid on establishing criteria for early diagnosis. This may have implications on the success of clinical trials, as the evidence obtained until now suggests that many therapeutic strategies could be beneficial if administered in the early or non-symptomatic phase of a disease.

DIAGNOSIS, THE CONCEPT OF MILD COGNITIVE IMPAIRMENT (MCI), BIOMARKERS

The diagnosis of AD is based on the presence of dementia and the exclusion of other disorders with similar symptoms. It is especially important to identify coexisting conditions, e.g. depression, use of some medications, the thyroid gland abnormality, vitamin B_{12} or folate deficiency and cardiovascular disease and its risk factors which are all potentially treatable.

Wherever it is possible, brain-imaging scanning, CT or MRI, are recommended, to exclude tumors, or thrombus, or microinfarction and to support the diagnosis of AD. Neuroimaging findings, typical for AD, include some degree of atrophy in memory-related cortical regions of the brain, including temporal and hippocampal ones.

An onset of overt dementia is not a discrete event. Rather, there is a gradually changing continuum from healthy cognition to impaired cognition and dementia. Therefore, neuropsychological testing is needed to support the diagnosis, by assessing the types and the severity of cognitive symptoms. One of the most commonly used tests for screening in the general population is MMSE (Mini Mental State Examination).

The accuracy of clinical diagnosis varies from 50% (in the primary health care setting) to over 90% (in specialized clinics). The diagnosis can only be confirmed by autopsy.

Experiences from the clinical trials investigating novel pharmaceutical approaches show that the earlier a disease is diagnosed – the earlier the treatment can start – the more likely are positive effects of treatment on preventing progressive neuronal loss. To recognize persons at high risk for developing dementia (most commonly of Alzheimer's type), the concept of Mild Cognitive Impairment (MCI) has been introduced. MCI is defined as a stage of cognitive impairment severe enough to be noticed by others and registered on cognitive tests, but not enough to interfere with daily life (MMSE>25) (Figure 1). It is estimated that about 10%-20% of people aged 65 years and older have MCI. A significant proportion of them, but not all, will develop clinically overt dementia in the following several years. The question of great concern is how to establish indicators of progression from MCI to dementia.

Available neuropsychologic tests, including MMSE, show weak positive predicting accuracy. Efforts are therefore focused on searching for more specific options of neuropsychologic testing. Computer-assisted cognitive test batteries are also in progress for use in both clinical trials and nursing homes. Advantages of computer-assisted testing in monitoring cognitive changes, in comparison with the traditional one using paper and pencil, are more comprehensive and more sensitive outcome measures.

On the other side, the challenge is to develop comprehensive cognitive tests with respect to cultural diversity, suitable for use in cross cultural studies. This is important because it has been observed that the high iliteracy rate and low educational level in developing countries may result in the screening of cognitively normal elderly to be positive for dementia.

An area of active investigation are also biomarkers, such as neuroimaging techniques and cerebrospinal fluid (CSF) biomarkers. Particularly biomarkers indicating β-amyloid depositions in the brain, such as PET (positron emission tomography) scanning and CSF measurement of Aβ are thought to have the potential to identify asymtomatic or very mildly symptomatic individuals. This approach is based on the findings that amyloid depositions precede clinical symptoms by many years. The problem is that pathological processes in AD are not understood well enough to be directly measured with biomarkers or imaging outcomes and do not well correlate with clinical outcomes. For example, amyloid depositions in the brain can be found at autopsy of older people not showing symptoms of cognitive impairments during life. Expert groups therefore suggest that the simultaneous evaluation of cognitive changes, brain volume (of hippocampus region) and CSF biomarkers should be used in predicting which person has the greatest chance to develop dementia in a near future.

Sophisticated new neuroimaging technologies, such as PiB (Pittsburg Compound) – PET, PET scanners equipped with the amyloid binding radiotracers, or FDG (fluorodeoxyglucose) – PET, PET scanners indicating impaired glucose metabolism in particular regions of the brain, have recently been established. Technological advances are expected to improve the feasibility of brain imaging in asymtomatic stage of AD and to allow functional neuroimaging. The latter means comparing changes in brain metabolism and patterns of neuronal activation with the type of mental activities, both in health and disease state.

The levels of neuropeptides in both CSF and blood have been shown to correlate with the extent of brain amyloid deposition. To avoid measurement by more aggressive lumbal puncture and to facilitate biomarker research in a more simple and patient-friendy approach, a number of molecular diagnostic techniques are under development using peripheral blood as a sample material.

Except for diagnostic purposes, biomarkers are valuable in selecting subjects for clinical trials as it has been shown that patients with AD differ among themselves regarding subtle pathobiologic characteristics, response to treatment and clinical course.

An emerging area of biomarker application is shortening phase III clinical trials during drug investigation. Actually, large and long-term studies should be conducted to show the effect of medication on slowing clinical progression or delay the time of diagnosis. In this situation, biomarkers could be validated as a surrogate endpoint.

Difficulties in establishing biomarkers for tracking disease progression can arise from the observations that a large number of non-demented elderly individuals have brain amyloid at autopsy. In addition, some of the people with subtle memory symptoms can revert to the healthy, some of them remain the same, and some proceed to dementia. There is a poor correlation between clinical stage and the type of dementia and the patterns of neuropathologic and neuroimaging changes. For this reason, joined international initiatives in the form of large longitudinal studies, are underway with the aim to provide more clearer answers about which individuals are likely to develop AD and when it is likely to happen. One of the most respectable and best funded initiatives is ADNI (Alzheimer's Disease Neuroimaging Initiative).

RISK FACTORS, GENETICS, MULTIFACTORIAL ETIOLOGY, COGNITIVE RESERVE

Alzheimer's dementia is considered as a chronic aging disease and is distinguished from normal aging. Most cases are aged 65 years or older (a late-onset disease), although an overt dementia in some cases appears under the age of 65 years (younger-onset or early-onset disease). These are predominantly cases caused by rare genetic mutations, linked to amyloidogenic and tau pathologic pathways.

Only one susceptibility gene for common, late-onset AD has been identified until now. This is apolipoprotein $E\varepsilon_4$ ($APOE_{\varepsilon 4}$), one of the three variants of the APOE4 gene whose protein products normally serve as carriers for circulating cholesterol. Over the last few years, large scale Genome Wide Studies have been undertaken to identify new susceptibility genes. However, it is likely that there will not be any novel single gene responsible for the development of AD, but rather multiple gene alterations characterize the disease. Based on these observations, gene-expression profiling techniques, performed on blood samples, have been emerging. This is thought to be a promising method for screening of the general population for the early diagnosis of AD.

Results of epidemiologic studies are convergent to those from studying genetics, indicating that AD, like other common aging diseases, is probably a result of multiple environmental factors acting on DNA sequence through epigenetic mechanisms. Lifestyle and cardiovascular risk factors, including high blood cholesterol, diabetes mellitus, hypertension, high blood homocysteine levels and low physical activity, have also been identified as risk factors for AD.

The great impact of environmental and socioeconomic factors on the expression of AD is illustrated by the fact that the variable »fewer years of education« significantly increases the risk of developing dementia at older age. Fewer years of education may be a surrogate marker for more complex socioeconomic factors affecting access to education. Also, this factor may reflect the level of occupational activities and lifestyle conditions associated with mental and physical health.

Cognitive Reserve Hypothesis (Stern, 2002) could provide a reasonable explanation for this association. This hypothesis has been established to explain observations that a number of patients with extensive brain neuropathologic changes are able to perform to a considerably higher level in clinical and neuropsychological examinations. The Cognitive Reserve Hypothesis states that an ability to cope with the brain pathology and to maintain normal neuropsychological performance is likely to depend on the capacity to recruit alternative neuronal networks. Surrogate markers for this capacity, termed cognitive reserve, have been identified and include the level of education and occupational activities, premorbid intelligence quotient and an overall cognitive and mental-stimulating activities.

VASCULAR COGNITIVE IMPAIRMENT

The brain is one of the most highly vascularized organ in the body. For this reason, cardiovascular disease and its risk factors affect also the brain and influence the risk for developing cognitive impairment and dementia.

Neuropathologic changes associated with vascular dementia generally differ from that in AD (mainly caused by neurodegenerative processes) and include large- and small-vessel disease, white matter lesion, micro-infarction and micro-hemorrhage.

However, there is a large degree of overlapping between AD and vascular dementia, best demonstrated in the form of mixed dementia (Table 1). The main proposed mechanisms by which vascular dementia and its risk factors accelerate brain atrophy are cerebral hypoperfusion, increased oxydative stress and reduced glucose metabolism. There is a growing body of evidence suggesting that cardiovascular risk factors may, by sharing molecular targets, affect both vascular and neurodegenerative pathogenetic pathways.

The relationship between vascular risk factors, cognitive impairment and dementia risk is an emerging field of research, especially with respect to the early phase of cognitive impairment and subclinical cardiovascular disease.

The question that needs a definite answer is whether prevention/reversal of cognitive symptoms may be achieved through vascular risk factor management and treatment. This is of particular interest because earlier

detection of cardiovascular risk factors and advances in therapy of cardiovascular diseases in the last decades, including the widespread use of new drugs such as statins and ACE-inhibitors, have taken part in the decline of mortality and the increase in the prevalence of these disorders. How these two opposite trends, increasing prevalence, in parallel with improvements in the treatment of cardiovascular disease and its risk factors, can affect the rates of dementia – is unclear at the moment.

In general, evidence suggests that clear separation between neurodegenerative and vascular pathobiology is not possible. The occurrence and the patterns of cognitive impairments and dementia are likely to be influenced by the existence of vascular diseases (including type, severity and duration), other co-existing conditions and underlying vulnerability, including age, education, positive family history of dementia and genetics. It is presumed, therefore, that one single strategy is not enough to prevent/cure cognitive disorders, but rather a combination of strategies will be needed, including lifestyle changes, multi-target medications, counselling, support groups and occupational therapies.

SOCIAL AND ECONOMICAL IMPACT OF ALZHEIMER'S DISEASE AND OTHER DEMENTIA

Alzheimer's disease and other dementia are devastating for patients and exhausting for those who care for demented people. These are, in most cases, family members. They often suffer emotional stress and are under the pressure of financial burden. Except of caregiving-related expenses, the financial loss to caregivers includes the reduction of their work hours or taking time off because of caregiving duties. Moreover, about one-third of caregives have symptoms of depression and are more likely to get hypertension and coronary artery disease.

Some demented patients require long-term care services, including nursing home care, mostly because of the exhaustion or inability of family members to provide care. The costs of long-term care place a burden on private financial resources and have a substantial impact on the healthcare system.

The capacity of long-term care institutions and the extent of the network of formal services for the elderly and demented persons depend on the healthcare system and the economic power of the state. Even in developed countries, a huge lack of health care workers and professionals with training in geriatrics can be observed. Health care staffing and development of support programs will be a challenge in the future as the number of people aged 65 and older is expected to grow.

It is estimated that pharmacological treatments and caregiver interventions, if started early, delay the need for nursing home placement and reduce the costs of caregiving. However, many patients with dementia are not diagnosed at all or are diagnosed at late stages of the disease. This can be attributed to several factors, including: low public sensibility for the problem, the prevailing fatalist perception that nothng can be done with such patients, the lack of physicians' knowledge abut dementing illnesses, the absence of recommendations for broader cognitive screening, only limited effects of available medical treatments and the absence of networked support programs.

Current efforts of the research teams to make a substantial therapeutic breakthrough in neurodegenerative diseases, along with the progress in imaging techniques, biomarkers and other techniques aimed at improving early diagnosis, are axpected to drive future advances.

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