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ALZHEIMER DISEASE

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OBSAH

1. Definition of Alzheimer disease, history.

Development of exact definition of Alzheimer disease was not straightforward and is still under the ongoing progress. Senile dementia has been well recognized by some physicians already in the first half of 19-th century. Alois Alzheimer, Munich neuropathologist in 1907 has described histological finding from the brain of Mrs. Auguste D. She died only in her 51 years with diagnosis of severe dementia after four years since the beginning of disease. Rather than Alzheimer himself, his colleagues considered the histological finding that brought discovery of neuronal droplets so different from the "common" senile dementia, than they enforced concept of Alzheimer's disease.

Major studies conducted in Europe and the United States over the following decades have shown that there are no quantitative histological differences between pre-senile clinical Alzheimer's disease and senile Alzheimer's dementia. The concept of senile dementia of the Alzheimer's type was introduced to distinguish other causes of senile dementia. Since the mid-1970s, the concept of Alzheimer's disease has begun to be promoted for both its different forms - pre-senile and senile.

Molecular genetic research in the past decade has shown that Alzheimer's disease is in some cases largely a common clinical, neurophysiological and neuropathic outcome of several types of gene disorders.

2. Familiar and sporadic form of Alzheimer disease

Approximately 10% of patients suffer from a genetically conditioned familial form of illness, with the first signs of dementia being observed after the 40th year of life. Familiar Alzheimer's disease (FAD) is a monogenic disease characterized by autosomal dominant inheritance. This is characterized by the high penetration of one of the four genes: the 21 chromosome amyloid precursor protein (APP), the chromosome 17 tau protein gene, the chromosome 1 presenilin 2 gene, and the chromosome 14 presenilin 1 gene.

Mutation of the presenilin 1 gene represents the major genetic defect in the FAD, which condition the early onset of the disease. Presenilins are transmembrane proteins that are not yet fully known. Current knowledge suggests their close relationship to the enzyme secretase, cleaving intramembrane sections of transmembrane proteins. It can therefore be deduced that

mutations in presenilins leading to accelerated Alzheimer's disease lead to the predominant in the neuron membrane (see below).

Other cases of the disease occur as a sporadic (late) form, without previous familial occurrence. In this case, clinical signs of onset of dementia usually appear in a risk group of persons over 60 years of age.

The development of Alzheimer's disease significantly affects some risk factors such as increasing age, overweight, hypercholesterolaemia, type 2 diabetes, and women are affected twice more often than men.

3. Patophysiology of Alzheimer’s disease

3.1 Clinical normal aging versus Alzheimer‘s disease

Clinically normal aging decreases both weight and brain volume. The decrease is particularly evident after the age of fifty-five. With age, the thickness of the cerebral cortex is reduced especially in the frontal lobes, less in the lower temporal region. After sixty years of age, the brain chambers expand. The number of neurons decreases during normal aging only in some regions of the brain, in addition to varying degrees, in many areas of the brain does not decrease. It is found that the fundamental change that accompanies clinically normal brain aging is far more neural reduction (atrophy-free) than their numerical decrease (numerical atrophy). The numerical decrease in brain neurons is apparently significantly lower than previously assumed. In the frontal cerebral cortex, between the 24th and the 100th year of life, fifteen percentage, in the upper temporal cortex ten percentage. In the hippocampus, about 80 years of age are approximately 20% less neurons than the average age of 40 years. Also, the number of Purkin's cells will decrease by about 20% between 20th and 90th year of life.

Functionally more significant than numerical atrophy of neurons is the involvement of dendritic neural systems, including their dendritic thorns, truncated structures visible in a light microscope during the use of impregnation methods during clinically normal aging. Thorns are post-synaptic parts of synapsis, sites of mutual neural interactions. Dendritic systems of neurons under the influence of external and internal stimuli grow in length, branching out, building new transient and relatively permanent synapses. The synapses are

highly plastic, functionally and structurally variable. It is assumed, that synaptic plasticity is basis of all activities of the brain, for instance learning and memory.

During clinically normal aging are documented both progressive changes of dendritic systems of brain neurons (growth to the length, branching, increase of numbers of dendritic thorns), as well as regressive changes (loss and shortening of branches, loss of dendritic thorns). In some areas of the brain, both types of changes are in a certain balance type up to the 10th decade.

During Alzheimer's disease, numerical atrophy of neurons exceeds clinically normal aging by 40-80%. Most affected area is temporal lobe, in next areas has been neural numeric atrophy described in some hypothalamic and thalamic nuclei, in retina and in nuclei of olfactory neuron.

Very remarkable and significant changes during Alzheimer disease are **regressive changes of dendritic systems** of some parts of hippocampus in comparison to clinical normal aging. In addition, a significant decrease in the number of synapses in the bark of the frontal lobe has been documented. The reason why the neurons disappear during Alzheimer's disease is unclear.

3.2 Extinction of brain neurons in Alzheimer's disease

The pathophysiology of Alzheimer disease is characterized by progressively degenerative damage of neural cells, mainly neurons and their synaptical connections, which is in initial phases of the diseases accompained only with small deficit of cognitive function. Development of the disease is than associated with gradual loss of memory, expressing skills, lost of mental functions, sometimes have changes of behavior psychotic character. The illness usually ends width death after 3-8 years of first manifestations of clinical symptoms. As with others dementias with neurodegenerative origin, Alzheimer’s disease causes the degeneration of certain existing brain proteins, and on the contrary, the formation of new pathological proteins.

Most authors consider the **wrong metabolism of the transmembrane glycoprotein, so called amyloid precursor protein (APP)**, to be the primary cause of the disease. APP is an transmembrane protein, a single gene product (locus is situated on 21-th chromosome). Its structure corresponds essentially to the membrane receptor. It is composed from 695 – 770 amino acids; variability is given by splicing variants. In neurons plays transmembrane APP role in synaptogenesis for embryonic development, and it has undoubtedly a number of

functions associated with the transmission of excitements and neural protections to various types of damages.

APP is in normal situations cleaved primarily by alpha-secretase into a soluble non-amyloid graft composed of thirty nine amino acids. This “spin” amyloid pre-cursor alpha (sAPP alpha) is probably responsible for the formation of neural thorns and its presence is considered to be a protective factor.

Under pathological circumstances , beta-secretase predominates, producing a protein residue of 82 amino acids, and then, by means of gamma-secretase, amyloid insoluble fragments (Figure 1). Both beta and gamma secretases cleave APP in normal conditions, but only small, insignificant amounts. According to the number of amino acid residues we distinguish more toxic A-beta 42 and A-beta 40 fragment.

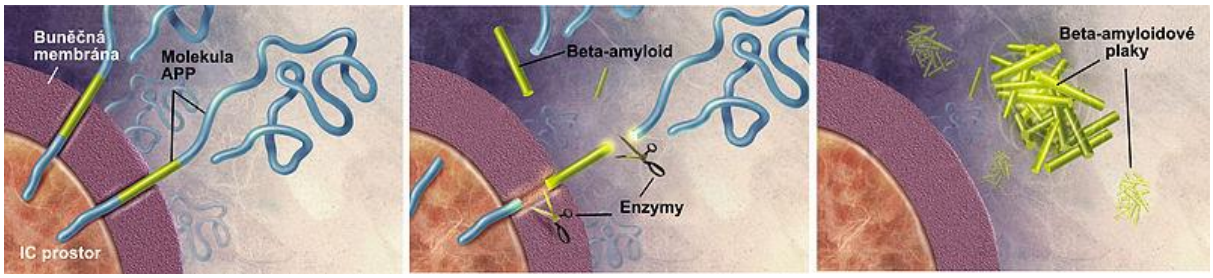


Fig.1: The yellow section of the APP molecule is cleaved with beta and gamma secretases, insoluble fragments become the basis for beta-amyloid plaques.

Peptide A-beta tends to misplace and to increase vascular wall deposition, resulting in the development of amyloid angiopathy and increased risk of bleeding into the brain. In the neurons, predominantly the A-beta 42 fragment accumulates, which initiates an oxidation process that damages normal nerve cell functions and causes degeneration.

However, neurotoxicity well above the level of A-beta 42 itself increases primarily the accumulation of oligomers and A-beta polymers. Their toxicity is related to the activation of the cascade of enzymes responsible for oxidative stress, which disrupts the homeostatic control of free CA2+ levels within the cell.

Elevated free oxygen radicals cause different degradation of the tau protein isoforms, whose altered ratio and increased phosphorylation make their release from microtubules, which disrupts the cellular cytoskeleton and leads to the extinction of the nerve cell. The result is the loss of ATP, a substance that has a bulk of energy in its macro-energy bonds. The resulting lack of energy. Free oxygen radicals release primarily inflamatory-activated microglia cells on the periphery of amyloid plaques. The resulting lack of energy of neurons resolves by programmed death, **apoptosis**.

Dysfunction and subsequent extinction of neurons are accompined by histomorphological changes. In the neurons and beyond, A-beta fragments are accumulated into microscopic fibres. Subsequent deposition of these A-beta amyloid plaques regurarly precedes the accumulation of the tau protein within neurons in the form of fibrils forming the neurofibrillar tangles. They contain abnormally coiled and hyperphosphorylated protein tau, which is mainly observed in sporadic forms of Alzheimer’s disease

At the microscopic level, nerve cell loss, loss of dendrites, their branching and synapses are evident. Classical amyloid plaques are spherical formations with a beta amyloid score surrounded by dystrophic neurite terminations. The neurofibrillary bundles are located intracellulary and from the filament of the hyperphosphorylated tau protein associated with microtubules (Figure 2). Histomorphological changes are associated with decreased release of acetylcholine (Ach) from nerve endings in the cerebral cortex and limbic system. Reduced release of Ach is associated with a decrease in the activity of the transport system, which is responsible for the accumulation of Ach in the synaptic nerve endings.

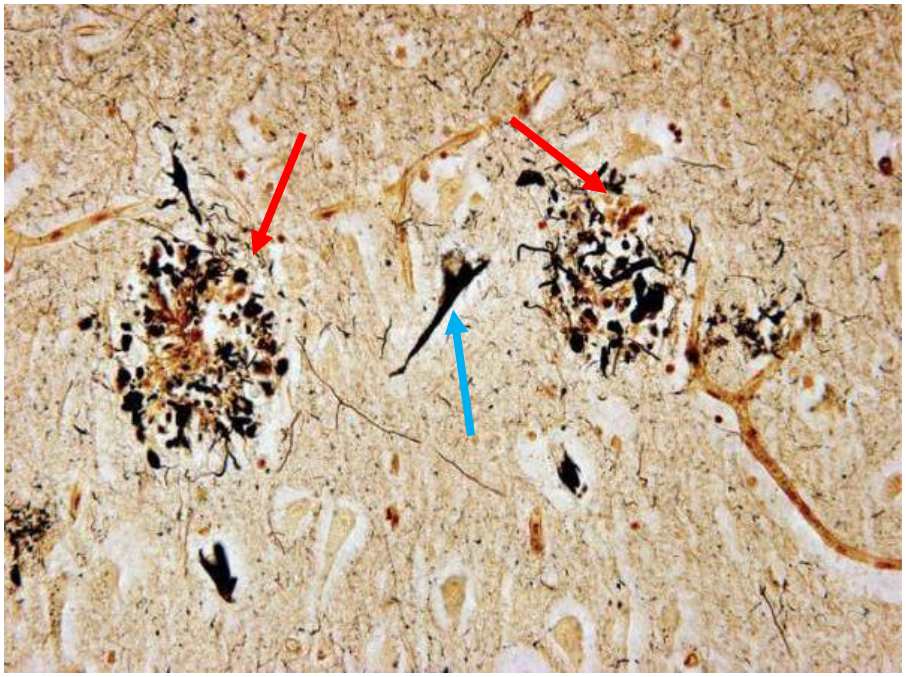


Fig.2: Histopathological image of the patient's cortex with Alzheimer's disease, two senile plaques (red arrows) and neurofibral tangle between them (blue arrow) – Bieschowski staining has been used, magnification 400x.

Extensive extinction of damaged neurons occurs primarily in some cortical regions (enthorhinal cortex, middle temporal gyrus) and subcortical structures (Maynert basal nucleus, hippocampus. The main macroscopic change is the atrophy of the brain tissue with the enlargement of the sulcus and chambers (Figures 3,4). Atrophy affects the entire cortex, while the occipital region is relatively well preserved.

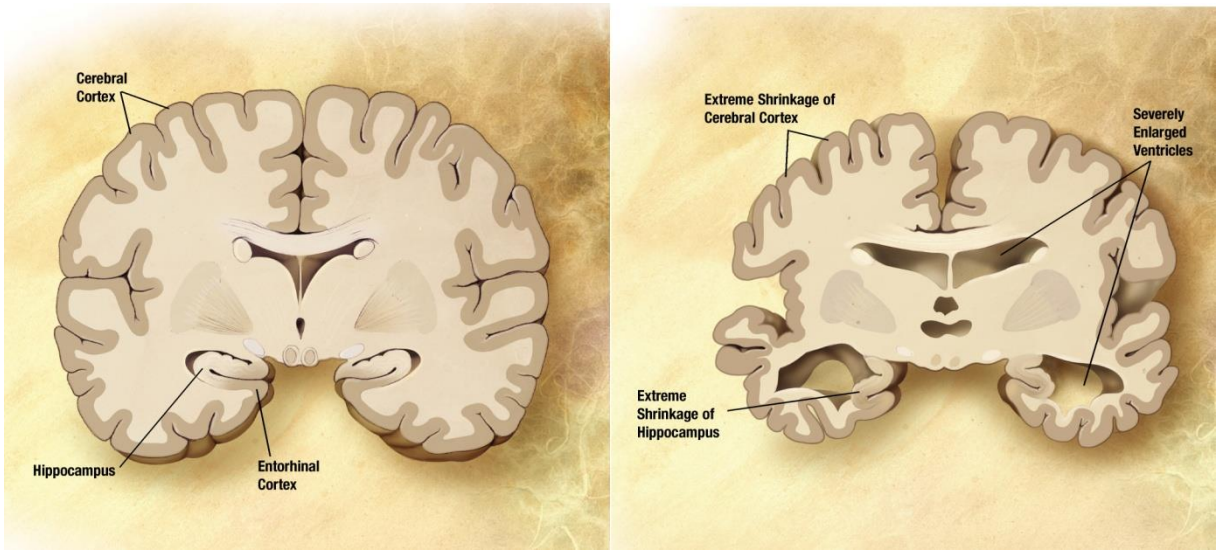


Fig. 3: Schematic of atrophic brain changes in advanced Alzheimer's disease

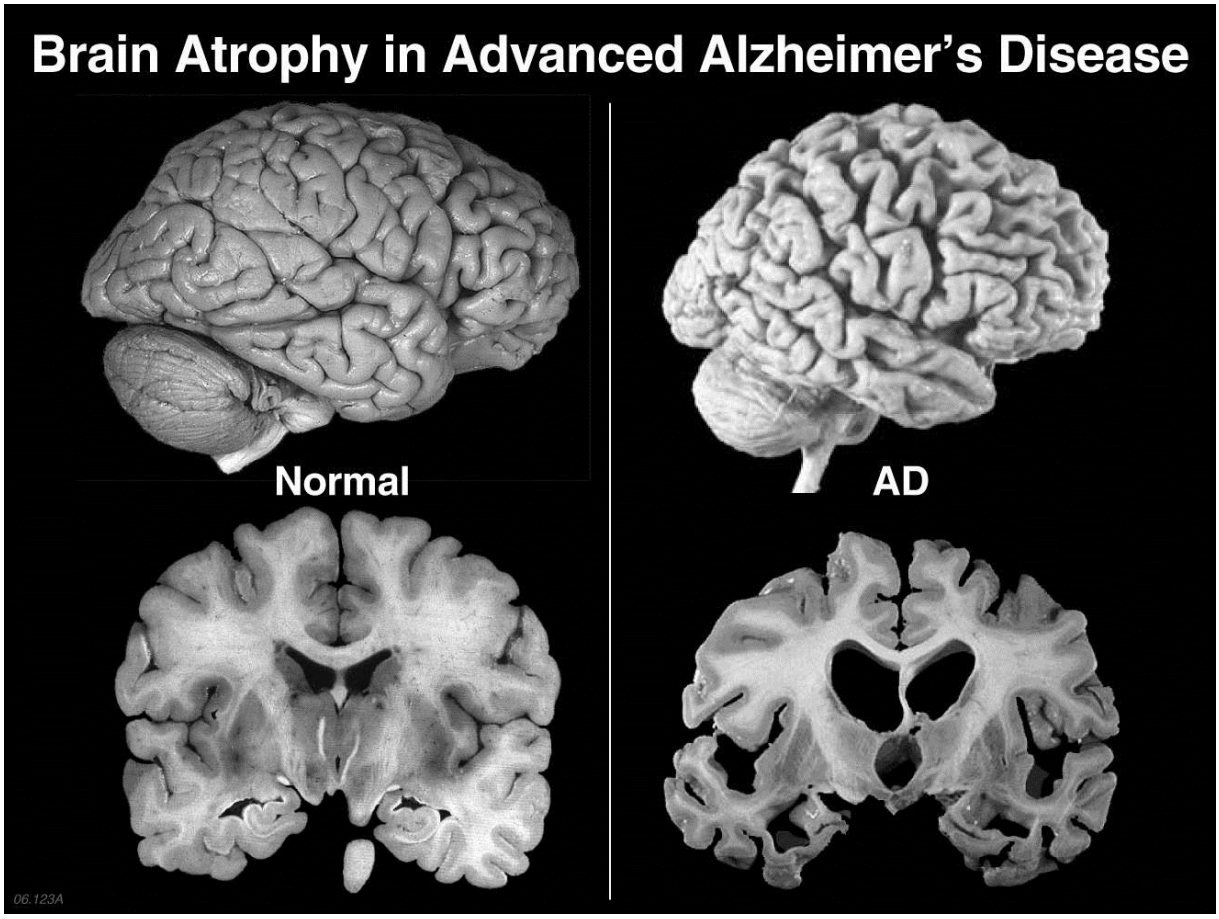


Fig. 4: Comparing the brain of a healthy and afflicted with the advanced phase of Alzheimer's disease.

4.Clinical symptoms of Alzheimer's Disease

The disease develops gradually. Recognition of first memory deficits from symptoms that may accompany clinnically normal aging may not be initially simple. It is not so clear,

how the first pre-clinical stage of the desease develops. Histological studies suggests that it is at least several years, but maybe several decades.

The first symptom, that initially distinguishes the patient or his surroundings is the **failure of recent episodic memories for words.** It manifest itself by forgetting everyday events. The patient does not remember what he had for lunch, where he wanted to go, who he met, what he read in the newspaper, whether he had it at all .

The **speech disorder** is another symptom. Speech is fluent, but empty in content, patients very often seek words. Behavior of patients, unlike in patients with frontotemporal dementia type, is socially feasible.

In that time disorders of the **visuospatial functions** express very often. The patients begin to wander, do not find their way home, forget how to go to places that have been visited for decades, such as mail or shop.

Some of the patients have more or less obviously affected **functions related to frontal lobes.** They will cease to be able to plan and sequencing even very simple activities. In approximately 40 % of patients begin to experience progressive non-cognitive impairment, for example **depression, halucination and agressivity**. Anosognosis is quite common, patients are convinced that there is nothing with them and they refuse treatment. In the course of further development the majority of patients are experiencing behavioral disorders manifesting uneasiness and wandering, confusion of objects and persons, paranoid delusions and hallucinations. Common are also disorders of sleep where structure of sleep is defragmented. Insight into the disease disappears proportionally to the progression of the disease – the more advanced the disease, the smaller insight patients have.

There are clinical and neuropsychological differences between the early (beginning of symptoms) and late forms of Alzheimer's disease (beginning of symptoms after 60th year of age) are clinical and neuropsychological differences. Earlier onset of the disease is characterized by greater damage of language, apraxia and higher incidence of depression, but the duration of illness is approximately the same.

Alzheimer's disease usually takes 3 to 8 years, man die earlier than women. Faster development of dementia and earlier deaths is reported in people suffering from heavier aphasia: a higher degree of disability of language functions is predicted similarly to the occurrence of primitive reflexes of earlier death. Part of the patients lose weight during the disease. Weight loss is believed to be related to the changes that occur in some patients in the hypothalamus.

In the advanced phase of the disease, patients' ability to communicate with the environment is diminishing. The patients have aphasia, they do not recognize friends and relatives, they are not capable to keep eye contact with people, incontinency is very common.

Alzheimer's patients die as a cause of death due to degeneration as case of bronchopneumonia, injuries and other immediate causes as a result of which the same old man would not die without this disease. Hypothetically there is a failure of neurohumoral homeostasis, failure of body adaptation and immune response. Patients sometimes die of injuries not suffered by the same old man without the presence of Alzheimer's disease, such as a patient who walked in the care of caring wife, sneaked on the sidewalk without making a single defensive move, and suffered a fracture of the cranial base.

5. Diagnosis of the Alzheimer’s disease

First, a diagnosis of the dementia is required. This diagnosis can be performed by both **clinical examinations** and **anamnestic data**, as well as by a **screening test**. However, some tests may give false negative results, the most useful of which is the more complex cognitive assaying test ADAS - cog (Alzheimer disease assesing test - cognitive component).

Diagnostically important is the course and clinical picture of dementia - slow progression, linear progression of deterioration, episodic memory disorder and gradually other components of memory, early personality decline, etc.

So called disease markers are used for confirmation of the disease. Main markers are:

- Imaging methods (CT – computer tomography, MRI – structural magnetic resonance) can discover atrophy of medial temporal lobe structures (hippokampus, amygdala) with the expansion of the ventricular system, especially the temporal corners of the lateral chambers (Figures 5, 6).
- When examining PET (Positron Emission Tomography) and SPECT (Single Photon Emission Computed Tomography), there is a reduction in the metabolism of brain tissue diffusely in the gray matter, but the findings are non-specific (Figure 7).
- The change in the ratio of some proteins (biomarkers) to non-Alzheimer's controls in the blood - increased levels of tau- and phosphorylated tau protein, reduced levels of beta-peptide 1-42.
- Episodic memory disorders as initial cognitive impairment.

There are a number of other Alzheimer's markers that are less specific than the previous ones.

However, the **definitive diagnosis** of the disease is only a **histological** diagnosis.

In recent years, there is a clear need to shift research efforts towards the pre-clinical stages of Alzheimer's disease and to search for biomarkers that could testify to the risk of dementia and allow research in the very earliest stages of the disease. Currently, most scientists believe that pathological changes in metabolism and amyloid deposition occur at least 10 years before the first clinical manifestations of the disease, whereas biomarkers of neuronal damage are generally positive several years later.

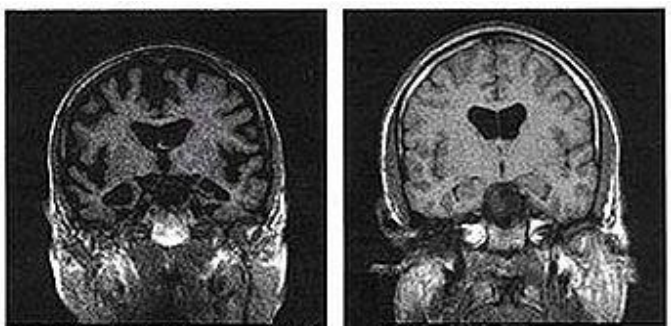
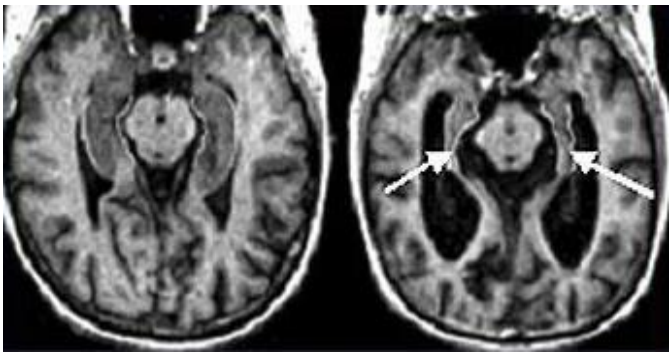


Fig. 5: Brain view using MRI, left atrophy in Alzheimer's disease, right normal finding.



Obr. 6: Zobrazení mozku pomocí MRI, vlevo normální nález, vpravo šipky označují atrofii hipokampální formace u Alzheimerovy choroby, patrné též rozšíření postranních mozkových komor.

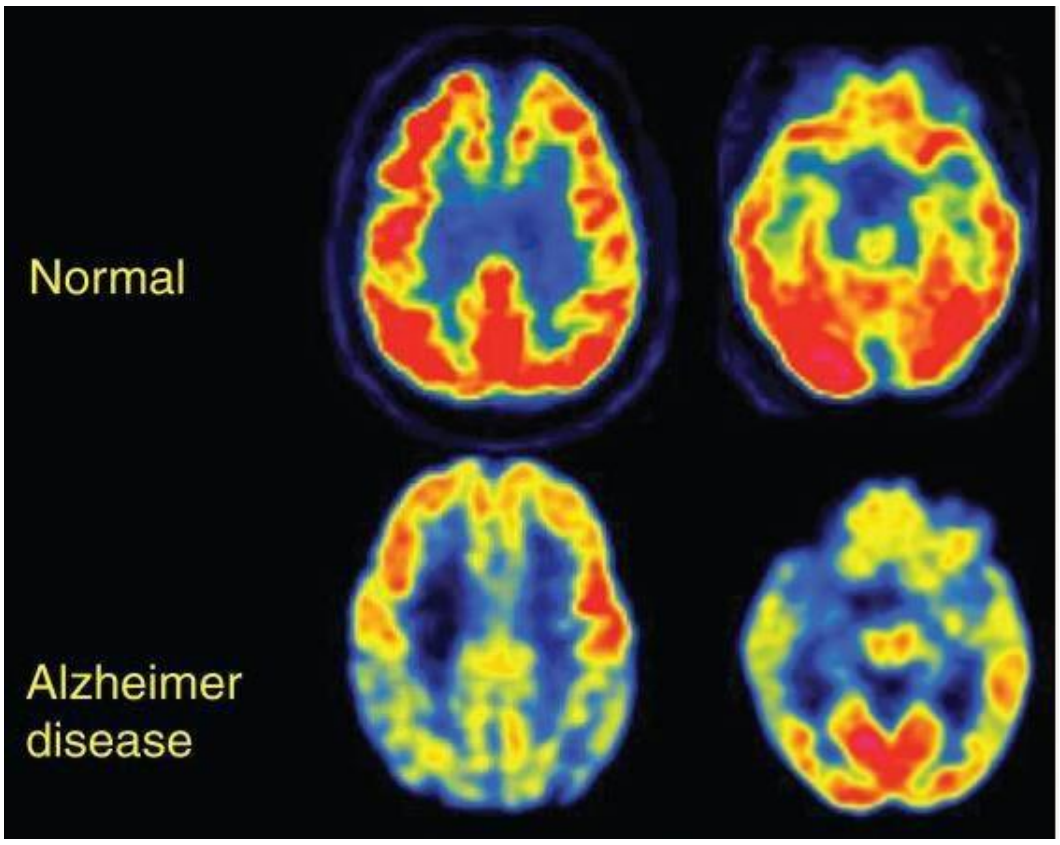


Fig. 7: PET imaging, comparison of a normal control patient with a mild form of Alzheimer's disease.

6. Therapy of the Alzheimer disease.

The complete etiopathogenesis of this disease has not yet been elucidated. Therefore, the approaches that are currently used can only modulate, slow down the course of the disease. The main effect, in addition to improving the quality of life of patients**, is the delay**

of severe stages of illness, associated with non-availability and subsequent institutionalization.

Pharmacotherapy can be divided into **cognitive pharmacotherapy**, which affects cognitive impairment (this therapy is closer to causal treatment) and **non-cognitive pharmacotherapy**, affecting primarily the behavioral and psychological symptoms of dementia (use of antipsychotics for behavioral disorders and associated psychotic symptoms, modern antidepressants in associated depression).

Cognitive pharmacotherapy is sometimes referred to as a therapy modifying the clinical picture of the disease. Only two approaches are based on "evidence-based" evidence: je v současnosti označována někdy jako terapie modulující klinický obraz choroby.

- Inhibitory mozkových cholinesteráz. Cholinesterase inhibitors. These drugs lead to blockade of enzymes degrading in the synaptic cleavage of acetylcholine, thereby improving the disturbed acetylcholinergic transmission.
- NMDA receptor inhibitors of the glutamatergic system. Here is a only a single product - memantine. This drug is a partial inhibitor of NMDA receptors. These receptors are associated with the opening of ion channels for Ca2 + and Na + ions. In Alzheimer's disease a such influx of ionts causes excitotoxicity - excessive release of excitatory amino acids (glutamate, aspartate), which then lead to the hyperexcitation of their receptors, including the NMDA type. In addition, this activity is increased by the decrease in glutamate reuptake in some regions of the brain (hippocampus). This leads to an excessive entry of calcium ions into the neurons, to the activation of some enzymes that alter the protein structure (protein kinases), to the increased expression of some genes, resulting in increased neuronal apoptosis (activation of programmed cell death of the neuron). Memantine significantly reduces excitotoxic action on neurons. Another positive effect of memantine is the inhibition of GSK3 protein kinase which triggers the degradation of the neuronal tau protein.

Treatment of Alzheimer's disease also requires psychotherapeutic and socio-therapeutic approaches. Reeducation therapies are important, we must try to practice with those functions that have remained preserved. A very important component of the treatment of the disabled is the work with their carers, usually the closest relatives.

6.1 The near future of therapy

The fact remains that all research efforts have not yet led to the discovery of any drug that would fundamentally change the fate of patients. The most important element in the etiopathogenesis of Alzheimer's disease is the formation and deposition of beta-amyloid protein. Beta-amyloid triggers another neurodegeneration cascade, including degeneration of the neuronal tau-protein.

The development of Alzheimer's drugs is in many ways, one of the most important being the pathogenesis of beta-amyloid. Therefore, beta-amyloid vaccination, administration of monoclonal antibodies to beta-amyloid, beta-gamma secretase, enzymes that cleave APP are tested. Unfortunately, some promising substances, yielding promising results in attempts

at mouse models of Alzheimer's disease, have made disappointment in human patients in recent years. Patient dementia appears to be the result of significantly more complex processes than amyloid plaque formation.

6.2 Preventions of Alzheimer's disease

The results of epidemiological studies suggest some options for the prevention of dementia, in particular some lifestyle factors, social contacts, mental and physical activity, dietary influences, as well as some possible preventive pharmacological interventions. Recently, the beneficial effects of flavonoids contained in coffee and especially in tea have been demonstrated; emphasis is placed on a balanced, fresh and varied diet respecting the principles of prevention of cardiovascular diseases. Based on the results of the studies and the meta-analysis of their data, it can be assumed that some drug groups (mainly calcium channel blockers) may prevent the development of cognitive impairment and dementia by a mechanism other than a reduction in blood pressure. This is to prevent prolonged calcium entry into the cell, and the rat model has additionally been confirmed that the calcium channel blocker of nitredipine in the brain blocks the channels preferentially in areas primarily damaged by Alzheimer's disease.

7. Individual forms of dementia

Dementia is a syndrome that arises from a brain disorder, usually of a chronic or progressive nature, which is disturbed by higher cortical functions, while consciousness is not obscured.

The greatest part of dementia is atrophic-degenerative dementia (about 60%), the most common of which is dementia in Alzheimer's disease. Vascular dementia is about 20%, the most common being multi-infarct dementia. Secondary dementia (in relation to trauma, infection, metabolic disorders of liver, kidney, endocrine diseases, tumors, etc.) is represented by 10%. Mixed forms of dementia represent the remaining 10%.

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