Clinical and Neurological Approach to Dementia of the Alzheimer's Type

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Abstract: Alzheimer's disease is the leading cause of dementia and is fast becoming one of the most costly, deadly and burdensome diseases of this century. Since the publication of the workshop in 2016, there have been important developments in the understanding of the underlying pathology, the recognition of multiple causative and protective genes, the identification of new blood and imaging biomarkers, and the first warning signs of positive disease effects. - modifying therapies and lifestyle changes.

Key words: Alzheimer's disease, blood biomarkers, warning signals, treatment, dementia.

Population aging is one of the most important problems of our century, which is now of great importance for the economy and social policy, not only in economically developed countries, but also in developing countries. The aging of the population has led to the fact that among patients of all categories, a significant proportion is made up of elderly and senile people, which makes the health problems of the geriatric population a priority [4].

The aging of the planet's population is an objective process, which is one of the most important problems at the turn of the 20th-21st centuries. Currently, the percentage of elderly and senile people in developed countries is quite large, for example, in Europe and the USA, there is one elderly person for six adults [5].

An increase in the number of this category of people in developing countries is expected, so by 2022 in China and India combined there will be 336 million people over the age of sixty, which exceeds the number of elderly and senile people today worldwide. Parallel to the growth in the number of older people, the percentage of people with dementia will increase. Currently, 18 million people in the world suffer from dementia, and by 2025 this number will increase to 34 million. This means that over the next 25-27 years, more than 2000 people a day will be diagnosed with dementia [1].

Dementia is a term that refers to impaired intelligence and memory in patients. Alzheimer's disease is considered to be the most common cause of dementia worldwide. Alzheimer's disease is a progressive neurodegenerative disease of the central nervous system with certain clinical and pathological
manifestations. (Kramer A, Kivipelto M, Johansson L, 2018) Pathological features for Alzheimer's disease are multiple cognitive impairments. The clinical picture of Alzheimer's disease fits into the "5 A" scheme: amnesia, aphasia, apraxia, agnosia, associated symptoms. Usually, the detection of Alzheimer's disease begins after 65 years. The number of patients is doubling every five years. Women are more likely to suffer from this disorder. The cause of dementia can be: vascular diseases of the brain, drug intoxication, alcohol disease, hypothyroidism, B-deficiency anemia, and others.

According to scientific research data, the need for outpatient care in older people is 2-4 times higher than in people of working age, however, the actual rates of seeking medical care at the prehospital stage of citizens of older age groups are only 1.5 times higher than similar data for the working-age population.

The hospitalization rate in the older age groups is about 165 cases per 1000 people, which is also slightly lower than the estimated need [5].

The need for hospitalization for certain types of specialized medical care (cardiology, endocrinology, pulmonology, urology, ophthalmology, neurology, psychiatry, and others) for older people is 1.5-3 times higher than for the working population. The need for medical and social inpatient care, according to calculations, is 49 cases of hospitalization per 1000 persons older than working age. (8)

The organization of medical and social assistance requires closer interaction between the bodies and institutions of health care and social protection of the population, and in some cases joint solution of the tasks set based on the integration of financial and other resources. Geriatric centers can serve as an example of such interaction.

Geriatrics is a separate area of medicine that deals not only with treatment, but also with patient care. Since older patients often have various diseases and disorders caused by aging of the body, the main goal of geriatric care is not to treat acute diseases, but to eliminate their symptoms, reduce the level of disability and preserve the functionality of the elderly person. (6) To maintain the necessary level of self-care for older citizens, medical care alone is not enough, since diseases and functional disorders that are present at this age are incurable. Almost every elderly patient needs help in everyday life. This assistance is usually provided by social institutions. Obviously, only effective cooperation between health authorities and social protection will fully meet the needs of elderly patients [Pushkova E.S., 2000].

Since we are talking about geriatric care, it should be noted that among medical problems a special place is occupied by senile dementia (vascular and/or Alzheimer's dementia), osteoporosis and its consequences (fractures of the femoral neck and spine), hearing loss and blindness, disorders urination and others. The listed medical problems in the elderly arose in medical practice before, before the stage of rapid aging of the population, but at present, senile dementia, the consequences of osteoporosis, diseases of the sense organs and incontinence are so widespread and the low effectiveness of traditional pharmacological methods of treatment that there is a need for new approaches to solving these problems. (10)

At the same time, in geriatric departments, very high demands are placed on nurses. A nurse with a higher education successfully performs the functions of a department administrator, whose duties include: selection of nursing staff, monitoring the work of nursing and junior medical staff, placement of personnel to solve the changing urgent problems of the department, equipping the department with solid and soft inventory, means of disabled equipment, medicines at the request of doctors, control over the sanitary and hygienic state of the department and patients.

Alzheimer's disease (AD) is the most common cause of dementia in the world and a major burden on the entire health care system. It usually develops in patients over 65 years of age. Due to the aging of
society, every year we observe an increase in the number of patients. More than 50 million people are predicted to suffer from AD dementia, and this number will triple by 2050. Pathological processes in AD begin at least 20 years before the onset of the disease, making it a chronic disease. (Koper MJ, Van Schoor E, Ospitalieri S 2020) The causes of AD are varied and not fully understood, and they are not properly correlated with the process aging. It is believed that both hereditary and environmental factors may contribute to the etiology of the disease. Less than 5% of all cases of AD are genetic, despite the fact that many gene mutations are associated with this disease. While sporadic late-onset AD (LOAD) is associated with the APOE 4 gene, early-onset AD (EOAD) is caused by mutations in presenilin 1, presenilin 2, and amyloid precursor protein (APP). Slow development of extracellular plaques composed of beta-amyloid and neurofibrillary tangles (NFT) composed of hyperphosphorylated tau are two histological indicators of AD. Therefore, they lead to the loss of synapses and neurons.

There is currently no known cure for AD, and preventive measures are being actively discussed. At present, the pace of clinical drug development for AD is low, and medical research is mainly focused on slowing the progression rather than curing patients. This is due to the not fully understood pathophysiology, the main features and the heterogeneity of the disease. (Plog BA, Nedergaard M. 2018)

The main pathological features of the disease include accumulation of beta-amyloid and hyperphosphorylation of tau protein. The consequences of these pathogenic processes include neurodegeneration with loss of synapses and neurons, which causes macroscopic atrophy. Mixed pathology, including vascular disease and Lewy bodies, is common, especially in the elderly [10].

Several cell types express a type 1 transmembrane protein known as amyloid precursor protein (APP). APP can sequentially cleave two different mechanisms in the central nervous system through gamma and beta secretases [7]. Aβ40 and Aβ42, two by-products of APP metabolism, are major components of misfolded amyloid plaques, which are extracellular aggregates. Due to increased fibrillation rate and insolubility, Aβ42 is more common within plaques than Aβ40 [14]. Aβ can then initiate a chain of events including neuroinflammation that causes synapse loss and neuronal death [Plog BA 2016]. Tau is a protein that is produced in neurons and which in healthy cells plays a role in maintaining the stability of microtubules in the cytoskeleton [Venegas C]. It accumulates inside the bodies of nerve cells as these NFTs become entangled through hyperphosphorylation. Cellular proteins, with which these tangles then interact abnormally, cannot perform their normal activities. Synapse dysfunction is due to a decrease in tau binding to microtubules. NFTs are produced in AD patients as a result of increased tau phosphorylation and intracellular tau aggregation caused by an imbalance between tau kinase and phosphatase activity. Finally, the development of NFT impairs synaptic plasticity [21], which damages neuronal cells. Studies show that the accumulation of Aβ can serve as a catalyst for the subsequent process of hyperphosphorylation [8]. There is also evidence that the toxic tau protein can increase Aβ production in a feedback mechanism [19].

Another recently described feature that is attracting a lot of attention is neuroinflammation. Although the mechanisms contributing to neuroinflammation in AD have been studied for over 20 years, they are still not fully understood. In the inflammatory response in the brain, microglia and astroglia are key players. Microglia can be activated and act in two types: M1 and M2. The M1 phenotype is considered “pro-inflammatory” and classic, while the M2 phenotype is considered “anti-inflammatory” and alternative [Reiman EM 2020]. Lipopolysaccharide (LPS), IFN, or TNF cause classical activation that is associated with pathogen defense mechanisms through the secretion of pro-inflammatory substances such as IL-1, TNF, and IL-6 and reactive oxygen species [Jonsson T, Atwal JK, Steinberg S]. Conversely, IL-4 and IL-13 induce the M2 phenotype, which releases neuroprotective substances such as TGF, IL-10 and IGF-1 [12]. Microglia M2 is able to enhance the remodeling and repair of brain...
tissues, regulating inflammation. Interestingly, the transformation of M1 to M2 can occur very quickly [17]. In addition, the pro-inflammatory environment created by active microglia around senile plaques promotes plaque development.

And not only microglia can be activated and affect the course of the disease. Interestingly, activated microglia are able to induce A1 astrocytes through the secretion of IL-1α, TNF and C1q [7]. According to one hypothesis, astrocytes can gather around plaques and beta-amyloid, which contributes to their activation. Studies have shown that the brains of AD patients and animal models contain active astrocytes [14]. Activated astrocytes give up their neuroprotective functions while causing neuronal and oligodendrocyte death by releasing pro-inflammatory cytokines such as TNF-α, IL-6 or IL-12 [20]. According to Liddelow et al. studies, A1 astrocytes secrete a neurotoxin that causes rapid death of neurons and oligodendrocytes [18].

An interesting aspect is related to iron dyshomeostasis. Many physiological processes in the human body depend on iron, but as we age, iron constantly accumulates in the brain. Early research has shown that cognitive decline in Alzheimer's disease is directly related to excess iron. Moreover, both APP and tau are associated with iron metabolism [11]. Iron is involved in the creation of neurotransmitters, myelination, and antioxidant enzyme activity in the brain [12]. It has been shown that an excess amount of iron accelerates the development of neurofibrillary tangles and senile plaques [17]. Moreover, a diet high in iron can cause cognitive impairment in mice, an increase in aberrant tau phosphorylation in neurons, and inadequate production of proteins associated with the insulin system. Supplemental insulin can reduce iron-induced tau phosphorylation [15], proving that iron accumulation can interfere with insulin signaling and cause tau hyperphosphorylation.

References


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