

Alzheimer's dementia

Keywords: dementia, consciousness, cognition, fatigue, memory

Abbreviations: AD, alzheimer's dementia; CRL, corticotropic releasing factor; APP, amyloid precursor protein; GPCPG, general practitioner assessment of cognition; MoCA, montreal cognitive assessment is applied; MMSE, mini-mental state examination; MIS, memory impairment screen

Mini review

Dementia is a disturbance of consciousness with a fully preserved wakefulness, manifested by multiple cognitive defects with memory damage without impairing consciousness. In patients with a disturbance of consciousness it is necessary to determine whether this is a matter of isolated damage such as amnesia syndrome or if this is a case of diffuse damages that are characteristic of dementia. It is also important to differentiate confusing state from dementia. Confusing state is characterized by acute or sub-acute beginning, fluctuating course with consciousness disturbance, attention deficit, increased psychomotorics, common reversibility lasting for several days or weeks, whereas dementia has a slow start, progressive course without disturbance of consciousness and without distraction lasting a few months or years accompanied by irreversibility. Dementias are acquired, generalized and most frequently progressive disorders of cognitive functions that include intelligence, learning and memory, speech, problem solving, orientation, perception, attention, concentration, judgement and social abilities. Strong personality damages can also occur. They are diagnosed if impairment of cognitive functions disturbs work and social functioning of a person and shows a deterioration from the previous level of functioning. In diagnostics along with common neurological testing it is crucial to test cognitive status involving examination of memory, attention, speech functions, sensory and motor functions as well as integrative functions. Clinically, dementias are manifested by changes in cognition, fatigue, difficulties in planning and performing tasks, personality changes, behavioural changes. Demented patients are prone to detailed and extensive retelling, anger, sarcasm, pathetic expression of the face, aggression and emotional instability. The disease ultimately causes complete disability and such persons require adequate care. Dementia is not exclusively related to the geriatric age, but it may also occur earlier with diseases that alter brain function. Causes of dementia may be different. The so-called „memo-VITAMINS test“ is applied and it indicates possible causes of dementia; these are vascular, infectious, toxic-metabolic, autoimmune, metastatic, androgenic, neurodegenerative and systemic causes. The most frequent is Alzheimer's dementia followed by a large group of dementias associated with parkinsonism involving dementia related to Parkinson's disease and dementia with Lewis relapses. Then follow vascular dementia, frontotemporal dementia, related tauopathies and many others.¹⁻³

Alzheimer's dementia (AD) is a progressive degenerative disease of the central nervous system; it is the most common type of dementia occurring in 5% of patients over the age of 50 and in 50% of patients over 80 years of age. It is also the most common cause of dementia in persons older than 65 years. The first and dominant disease symptom

Volume 2 Issue 3 - 2018

Tatjana Cikac,¹ Tea Haramija Poljak,² Ivan Poljak²

¹Specialist doctor in obiteljske medicine, croatia

²Doctor in medicine, croatia

Correspondence: Tea Haramija Poljak, Specialist doctor in obiteljske medicine, croatia, Email tea_haramija@hotmail.com

Received: April 09, 2018 | **Published:** June 12, 2018

is a memory disorder along with disorders of speech function, praxies, gnostics and executive functions. The consequence is emergence of disturbances in three key areas of life: in daily life activities, behaviour and personality as well as cognitive functions.^{1,2}

The cause of AD is unknown but it is considered to emerge by interaction of genes and environmental factors. Most frequently it occurs sporadically and in ca 5% of patients it comes about within the family where it is inherited autosomally dominantly with disease symptoms that appear before the 60. year of age. Until now three genes have been established responsible for emergence of hereditary form of disease: gene mutation for amyloid precursor protein on 21. chromosome, gene mutation for presenilin 1, transmembrane protein on 14. chromosome also called Alzheimer's chromosome and gene mutation for presenilin 2. Gene for apolipoprotein E4 on 19. chromosome increases proneness for Alzheimer's disease but it does not necessarily have to trigger off the disease. Trisomia 21 (Down's syndrome), translocation of chromosomes 21-24 or 21-21 increase incidence of Alzheimer's disease already after 40. year of age.^{1,3}

Pathological finding is characterized by observable cortical atrophy especially of hippocampal area and histopathologically it is characterized by neuritic senile plaques containing extracellular deposits of beta-amyloids, presenilin 1 and 2, apolipoprotein E and intracellular plaques of neurofibrillary fibers of hyperphosphorylated tau protein and ubiquitin protein. In the initial phase of disease neuritic plaques of spherical appearance are localized in hippocampus affected by atrophy and in later phase of disease these changes are localized in other cortical neurons. It is considered that in pathogenesis it comes to cascade of events, that is aggregation of proteins containing amyloid beta-peptide. This induces phosphorylation of tau protein and formation of neurofibrillary fibres which leads to oxidative stress, inflammatory changes, excitotoxicity, cellular death and consequential discontinuity of transmission and dementia development. An essential role play abnormal metabolism of beta-amyloids and their sedimentation. Pathogenesis includes three processes: pathological degradation of beta-amyloids and formation of neuritic plaques, inclusion of phosphorylated tau-protein and degradation of cholinergic neurons and acetylcholine –transferase. Beta-amyloid is a peptide formed by proteolytic decomposition of transmembranous amyloid precursor protein (APP) by activation of alpha-secretase and it consists of 40 amino acids that are normally eliminated from the brain. In AD, APP is abnormally decomposed with beta-secretase and afterwards it forms

with help of gamma-secretase abnormal beta-amyloid containing 42 amino acids and it leaves sediment in extracellular neuritic plaques as well as in blood vessels and meninx. In pathogenesis of AD except formation of neuritic plaques it comes to inclusions of phosphorylated tau-protein. Tau-protein is a protein responsible for axonal transport and balance between phosphorylated and non-phosphorylated form is required for its adequate functioning. The above-mentioned disturbances of beta-amyloids cause increased Ca entering the cells which leads to disturbances in phosphorylation of tau-protein that in certain areas becomes hyperphosphorylated and as such leaves sediment intracellularly. According to some theories such inclusions of hyperphosphorylated tau-protein are considered a key event in development of AD. In patients with Alzheimer's dementia it comes to degradation of cholinergic neurons and acetylcholine-transferase (consequently reduced synthesis of acetylcholine) in hippocampus and other parts of brain cortex. Bioptic material shows the biggest deficits of neurons in frontal and temporal cortex but in hippocampus as well and deficit of acetylcholine transferase directed treatment of AD towards its inhibitors. In mechanisms of disease development disturbance of noradrenaline metabolism is mentioned that takes place in frontal cortex and hippocampus as well as reduction of serotonin, dopamine and histamine. It also comes to changes in hypothalamic-hypophysial-adrenal axis in sense of increased activity causing damages of hypothalamus and consequential decrease of release of corticotropic releasing factor (CRL) that is considered responsible for reduction of cognitive functions. In AD hyperaldosteronism has been proved.¹⁻³

Risk factors for development of Alzheimer's disease are correlated with risk factors for development of cerebrovascular disease and they include arterial hypertension, diabetes mellitus, hyperlipidemia, systemic vascular disease, smoking, excessive intake of saturated fatty acids and calories, increased level of homocysteine, low level of vitamin B12. A few studies have shown that hormonal substitute therapy with estrogens in postmenopause reduces risk of AD development in 50% of women but administration of estrogens in people with already developed AD did not prove as useful. However, some studies have shown that administration of estrogens and progesterones or only estrogens in women older than 65 years even doubly increases risk for dementia development, most probably acting with vascular mechanisms.^{1,4}

Alzheimer's dementia is an insidious disease that develops slowly but continuously progresses throughout years. Disease starts mainly after 65. year of age but it may also start earlier depending on the fact whether this is a case of AD with an early or late beginning. In case disease starts before 65. year, it is manifested with a fast progression and observable multiple disturbances of higher cortical functions but if it starts after 65. year, its progression is slow and in early phase damage of recent memory prevails that is observed by family members in the beginning. By means of progression of memory disturbance disorientation is developed, first the time and later spatial one as well. Disease is manifested in numerous cognitive deficits that along with memory disturbance include at least one more cognitive disturbance. Aphasia (speech disturbance), apraxia (impaired capacity of performance of motoric activities), agnosia (incapacity of naming and recognising objects), disturbance of executive functioning (planning, organizing, adding, subtracting) and etc which makes work capacity for the patient impossible. Due to development of apraxia and visuospatial disorientation the patient gets lost easily in otherwise familiar environment. With a neurological examination we can find

primitive reflexes, disturbance of walk of frontal type, characterized by short steps and shuffling feet upon the floor and flexial posture of body, walk with wide "holding" of lower extremities and difficulty in starting to walk that is called apraxia of walk. It often comes to development of non-cognitive symptoms: depression, restlessness and psychomotoric agitation. In later phase of disease it comes to loss of social contact and non-cognitive symptoms that is mental disturbances dominate that become more and more often with disease progression. Sixty-four percent of AD patients are considered to have one or more behavioural or psychic symptoms that are a better predictor of speed of patient's accommodation in an institution than the level of cognitive deterioration. In clinical image psychotic symptoms that is insanity, hallucinations and delusions, mainly paranoid ones, are dominant. In demented patients with psychotic symptoms physical aggression and other types of violence are frequent, especially in patients with impaired frontal and temporal brain lobe. It comes to decreased capacity or incapacity of expressing a need for thirst quenching, hunger appeasing, need for a rest or sleep. If there are symptoms of bodily disease such as pain, constipation, dispnea, urine retention and others it may lead to psychic symptoms or behavioural changes as an AD patient cannot express what he/she feels and what difficulties he/she has. Psychic symptoms often hide symptoms of deterioration of bodily conditions or emergence of an acute disease. In neurological status rigidity and bradykinesia are noticeable and myoclonia and spasticity are possible as well. Patients become bed-ridden and incontinent. At the beginning of disease development the individual suffers most and with weakening of cognitive functions, sufferings of the family, that is individual looking after the patient are more observable.^{1-3,5}

According to Clinical Dementia Rating Scale AD is divided into three categories:

- i. Mild AD—Recent memory is impaired, difficulties in memory, finding proper words and complex cognitive functions crop up and the patient is unable to work. Loss of social contact is noticeable but the patient is independent in daily activities and hygiene maintenance.
- ii. Moderate AD—Orientation and insight into what's going on are impaired. The patient needs help in daily activities, often gets lost in familiar environment. Not rarely there are agitation and delusions including insomnia that is also noticeable.
- iii. Severe AD—The patient is completely dependent on other people's help in daily activities, he/she must be fed, dressed and washed. In later phase he/she becomes unable to move and completely bed-ridden.¹

Diagnosis of Alzheimer's disease is with 100% certainty made post mortem, with a finding of patient's autopsy. Clinical diagnosis is based on further anamnesis, records of initial and subsequent symptoms, behavioural changes, differential diagnostic approach and insight into psychiatric diseases, heteroanamnesis and general somatic neurological, neuropsychic and neurocognitive examination, laboratory findings and image methods. Insight into medicamentary therapy of the patient is required that might affect symptomatology. In patients with observable and clear symptoms along with positive family anamnesis diagnosis is made easily. Difficulties in diagnostics appear in initial phase of disease when the patient shows symptoms of mild cognitive disturbance and in this phase of disease tests oriented towards Alzheimer's dementia and other dementias should be carried out.^{1,3,5}

Routine neurocognitive examination includes so-called Mini-Mental State Examination (MMSE), validated for Croatian population but it is not sufficient as a comprehensive approach to differential diagnostics is required. MMSE test is conducted in 10 minutes and it comprises simple questions that examine naming of terms, short-term memory, visuospatial orientation and performance of basic motoric and mathematical actions. It consists of total of 30 points, each answer is scored and based on acquired results, degree of dementia is determined, interpretation is corrected according to the level of education and age and points limit less than 24 refers to cognitive impairment. Early recognition of mild cognitive damage is crucial as it enables identification of people that may develop dementia throughout years which is a leading and responsible role of general practitioner. Besides MMSE, for a quick selection of patients with mild cognitive damage Montreal Cognitive Assessment is applied (MoCA). It is often used as supplement to MMSE test, especially for milder damages since specificity and sensibility of cognitive selection are improved with combination of tests. The test lasts from 10-12 minutes and comprises examination of memory, language, attention, concentration, conceptual thinking, calculating, executive function and orientation. A test of drawing a watch can be used as well and it is informative, lasts shortly in terms of time and serves as a screening test for memory disturbance. In assessment of mental condition Mini-Cog test can be used that requires a couple of minutes and it comprises naming of three unrelated words and drawing a watch with particular position of its hands and repeated recollection of the three named terms. In practice of family medicine most adequate tests are those lasting maximum 5 minutes and they minimally depend on the level of education, language or ethnic background of the patient. These are General Practitioner Assessment of Cognition (GPCPG) and Memory Impairment Screen (MIS). GPCPG consists of 6 items, name and address, time orientation that is date of testing, drawing a watch and certain time, acquisition of information what has been going on recently and repeating of the name and address. MIS is based upon association of four named objects and their identification in particular categories and upon recollection of used terms.^{1,2,5}

Neuropsychologic assessment of demented people is an important step in diagnosis making. Standardized and highly specific tests as well as so-called neuropsychologic batteries made for gaining objective, quantitative measures and potentially qualitative differences in differential diagnostics of various types of dementias are applied. There are also aim-oriented sensible neuropsychologic tests that measure small changes in cognitive functioning and therefore we can detect changes characteristic of mild cognitive disturbance with their application.^{2,5}

Laboratory findings endeavour to exclude other causes of dementia. In algorithm of processing we examine thyroid gland hormones, vitamin B12, folic acid, VDRL/FTA in serum, HIV and borrelia testing. Basic biomarkers of disease, beta-amyloid (1-42), total and phosphorylated tau (P and T tau) protein are determined in liquor; however, they are not reliable enough for making an early diagnosis regarding the fact that values overlap with those in dementias of other primary causes and in normal ageing. For this reason there is an urgent need for detection of new markers in cerebrospinal liquor and other markers as well for making an early diagnosis of disease. In later phase of disease basic biomarkers show high specificity and sensibility for AD that means that low level of beta-amyloids and high value of P and T tau proteins in liquor appear by means of which AD differs from dementias of other causes and normal ageing.^{1,5,6}

Image methods MRI or CT of brain indicate cortical atrophy and increase of brain chambers although such finding is also obtained in elderly people that do not suffer from dementia. Besides this, MRI displays considerable hippocampal atrophy, SPECT displays reduced circulation in frontal cingular and left frontotemporal lobe and PET decreased metabolism of glucose in temporal regions.^{1,4} Treatment of Alzheimer's dementia encompasses medicamental therapy with antidementia drugs that improve cognition, make disease progression slower and improve the patient's general functioning. Treatment with antidementia drugs also considerably decreases emergence of behavioural and psychic symptoms, improves communication with the patient, enables larger and longer independence of the patient in daily life activities, which facilitates care for care-givers and postpones time of the patient's accommodation in an institution. Therapy includes inhibitors of acetylcholinesterase (AChE inhibitors) such as tacrine, donepezil, rivastigmine, galantamine that enable control of disease symptoms and slow down its progression and NMDA receptor antagonists—that is memantine protecting neurons from toxic activity of amino acids that cause their death. There is also a fixed combination of donepezil and memantine. From the group of acetylcholinesterase inhibitors, tacrine, galantamine and rivastigmin have been approved for treatment of mild and moderate AD (tacrine has nowadays more historical than practical meaning, especially due to its hepatotoxicity), whereas donepezil is intended for treatment of all three degrees of disease. First choice in treatment of AD is donepezil and if upon its administration no satisfactory therapeutic response is achieved, the second choice is rivastigmin or galantamine. Side effects of this group of drugs appear at the beginning of therapy and are as a rule mild and temporary, most frequently affect gastrointestinal system and are manifested as nausea, vomiting, diarrhea, anorexia, loss of weight. In this case slowing down of drug titration or not taking a few doses are recommendable. Among most frequent side effects there are insomnia, hallucinations, restlessness, incontinence and less frequently it comes to slowing down of heart rate due to which an EKG is recommendable before introducing therapy, especially in patients who suffer from AD and have positive cardiological anamnesis. New opportunity of antidementia drugs administration are transdermal flasters that improve collaboration of the patient and decrease side effects.^{1-3,5}

From the group of NMDA receptor antagonists drug memantine has been approved and it is foreseen for treating moderate till severe degree of AD. It shows improvement of cognition and daily functioning. Memantine is introduced gradually, first 5 mg in the morning. After a week another dose of 5 mg is added in the evening and then 10 mg in the morning and 5 mg in the evening for another week till maximum daily dose of 20mg. Combination of memantine with one of three inhibitors of acetylcholinesterase leads to a slower deterioration of cognition and daily functioning in AD patients unlike monotherapy with inhibitors of acetylcholinesterase. Memantine also has less side effects than AChE inhibitor and is mainly well tolerated. It is not hepatotoxic and is secreted through kidneys. Although there are no sufficient information about its harmful influence on kidneys, administration of smaller drug dose is recommendable in people with mild and moderate kidney failure, whereas in severe kidney insufficiency drug administration is not recommended. Antidementia drugs are necessary in treatment of Alzheimer's dementia and they represent a standard therapy as they improve cognition, facilitate patient's functioning, decrease behavioural and psychic symptoms, postpone accommodation in an institute, enable better communication, bigger patient's independence, facilitated care for care-givers

and affect decline in total expenses of treatment and care. Today antidementia drugs are available medicaments and do not belong to the group of expensive drugs but in the Republic of Croatia they are not on the A-list of drugs of Croatian Institute for Health Insurance. Therefore, majority of people suffering from dementia are not treated adequately as they cannot allow themselves additional payment for drugs that are recommended to them.^{1-3,5}

Besides common antidementia medicament therapy in treatment of Alzheimer's dementia we can approach in a completely different manner that includes psychosocial treatment, therapy of cognitive failures, therapy of psychosis and agitation, therapy of depressiveness, therapy of insomnia etc. In treatment of behavioural and psychic symptoms the approach is individual and non-pharmacological methods of treatment have a priority as a rule. Environment in which the patient is taken care of must be peaceful, adaptable, without strong stimuli (noise, many people, strong light) with routine changing at its minimum level. Physical activities of patients should be encouraged, the hyperactive ones given an opportunity to move and usage of signs for an easier spatial orientation as well as provision of doors, windows etc provided. It is crucial to assess the risk of suicidality and psychoeducation of the patient's family members or his/her care giver is required. Psychosocial treatment encompasses occupational therapy of the patient, memory drills and learning how to cope with existing deficits. Other types of the above-mentioned therapies are introduced depending on accompanying symptoms. Pharmacological approach is applied when other approaches are insufficient and when administration of drugs is necessary for the patient's safety and his/her environment. Hypnotics drugs, anxiolytic drugs, antidepressants, antipsychotics drugs and anticonvulsive drugs are introduced depending on the accompanying symptoms. Hypnotics drugs are used for treatment of insomnia: these are zolpidem, fluzepam, midazolam and nitrazepam. They are administered according to the need, but not continuously. Highly and lowly potent benzodiazepine drugs are used. From lowly potent ones oxazepam drug is used that is very well tolerated especially in elderly people and from highly potent lorazepam is most frequently used although studies have not singled out any of them as more efficient than the other from that group. Barbiturates are not used except in patients that do not react to benzodiazepine. Benzodiazepine drugs are as a rule used in extreme agitation with aggressive behaviour, stressful situations, panic attacks, they are prescribed for a brief period of time in order to sublimate anxiety. In elderly patients they cause side effects such as cognition deterioration, sedation, delirium, confusion, breathing deterioration, increased risk of falling. Antipsychotics drugs are used for treatment of psychotic disturbances and symptoms—delusions, paranoid and insane ideas, for sedation and control of irritability, emotional instability and restlessness. They are administered with caution, gradual titration and regular follow-up of the patient. Older antipsychotics, haloperidol and promazine are used in extremely agitated, aggressive and non-cooperative patients. They are evaded due to their adverse influence on cognitive functions and more frequent development of extrapyramidal side effects that make movements of the patient additionally more difficult. Without any indication for that antihypnotics of new generation have been used since 1990— risperidone, olanzapine, quetiapine, clozapine, aripiprazole drugs. Only risperidone drug was later registered as the only antipsychotics for treatment of AD patients but with duration till 6 weeks. New antipsychotics have less anticholinergic activities and less extrapyramidal side effects and they achieve mood stability with preservation of cognitive functioning. Studies have shown

increased risk of mortality in demented people due to more frequent cerebrovascular incident. According to the guidelines of American Psychiatric Association initial dose of risperidone drug amounts to 0,5-1mg and maximum daily to 1,5-2mg. For treatment of depressive symptoms antidepressants are used, among them most frequently inhibitors of repeated storage of sertraline-escitalopram, citalopram and sertraline, whereas tricyclic antidepressants are evaded. Except for the fact that they are indicated in depressive episodes, good clinical practice has shown that antidepressants help sublimate irritability and aggressive behaviour. Administration of half of the smallest common dose is recommendable. For treatment of insomnia zolpidem or alpidem are used. Anticonvulsive drugs are usually used in patients will mood oscillations, impulsiveness, disinhibited behaviour and in epileptic attacks; most frequently carbamazepine and Na-valproate. Their careful titration is also required. Administration of aspirins for better brain circulation, ginkgo products and vitamin E are often recommendable. Since hyperlipidemia is one of risk factors for AD development it was considered that statins have an essential role in treatment and sublimation of disease symptomatology. However, studies have shown that there was no significant difference in patients that used statins and those who used placebo.^{2,5,7}

General practitioner has an essential role in early detection of Alzheimer's disease, recognition of dementia symptoms, referring to diagnostics and specialist consultation, participation in treatment and follow-up of the disease, especially in organization of care and offering permanent help to the patients and support to the family in care of AD patients. He is a part of interdisciplinary team comprising experts of various work fields, specialist consultants, nurses, social workers, psychologists and other experts of various professional profile. General practitioner follows and understands patient's needs and demands for each person as an integral person from pathological, biological, social and psychological point of view in his/her environment. He offers patients continuous and comprehensive protection throughout long period, acquires insight into all health problems, social and family aspects of life and their influence on emergence of pathological conditions. Except for the fact that he cares for somatic diseases, he plays an important role in application of palliative care with aim of preserving mental health and early detection of changes of cognitive abilities and follow-up of health status of people with mild cognitive disturbances till the organization of treatment and further care for demented people. The role of physician enables implementation of strategy of Croatian fight against Alzheimer's disease and other dementias where an early diagnosis, treatment, care, destigmatization, offering help to families that care for the patient in his/her home environment. With his expert competencies he can organize team work and family in treatment of AD patient but also recognise situation when the family is unable to offer all necessary care for the patient. In such situations he can encourage the family in time to ask for and accept help of other expert workers of this field such as geronto-hostesses, patronage nurses, services of daily centre or accommodation in an old people's home.⁵

Acknowledgements

None.

Conflict of interest

The author declares no conflict of interest.

References

1. Brinar, Vesna. *Neurologija za medicinare*. Zagreb, Croatia: Medicinska naklada; 2009.
2. Frančišković T, Moro LJ. *Psihijatrija*. Zagreb, Croatia: Medicinska naklada; 2009.
3. Apostolova GL. Alzheimer disease. *Continuum*. 2016;(2 Dementia):419–434.
4. Imtiaz B, Tuppurainen M, Rikkonen T, et al. Postmenopausal hormone therapy and Alzheimer disease. *Neurology*. 2017;88(11):1062–1068.
5. Tomek-Roksandić S, Mimica N, Kušan Jukić M. *Alzheimerova bolest i druge demencije- rano otkrivanje i zaštita zdravlja*. Zagreb, Croatia: Medicinska naklada; 2017.
6. Counts SE, Ikonovic MD, Mercado N, et al. Biomarkers for the early detection and progression of alzheimer's disease. *Neurotherapeutics*. 2017;14(1):35–53.
7. Mejias-Trueba M, Pérez-Moreno MA, Fernández-Arche MĀ. Systematic review of the efficacy of statins for the treatment of Alzheimer's disease. *Clin Med*. 2017;18(1):54–61.