Dementia in old age – diagnostics, differentiation and current therapeutic management proposition

Otępienie w starości – diagnostyka, różnicowanie i aktualne propozycje postępowania

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Key words
Alzheimer's disease, frontotemporal dementia, vascular dementia, dementia with Lewy Bodies, pharmacotherapy, rehabilitation

Abstract
The disorder of higher functions of the core is characteristic of dementia, which often affects old people. It is mainly caused by Alzheimer's disease (AD), vascular dementia (VaD), frontotemporal dementia and dementia with Lewy's Bodies. Etiology of AD is still unknown. The most important risk factor are APOE 4 gene, age, sex, short education period, jobs that do not require intellectual activity and dementia among family members. The main pathomorphological changes consist in the presence of senile plaques and neurofibrillary tangles, whereas pathophysiological changes consist in disorders in cholinergic system. AD manifests itself in the insidious onset, a slow course of the disease, memory, spatial orientation and behavioural disorders, aphasia, apraxia, agnosia, dissomnia, difficulties in getting dressed and practising personal hygiene, and later on hallucinations, delusions, incontinent sphincters, increasing weakness and lack of mobility finally resulting in infections and decubitus ulcers. Vascular dementia is generally caused by cerebral ischaemia. The main risk factors include age, sex, hypertension, level of education, smoking, diabetes, and hypercholesterolaemia. VaD differs from AD with a sudden onset, an irregular course of disease, criticism and mood depression. It is more frequent in men. Dementia with Lewy Bodies takes a course with intensified extrapiramidal disorders, whereas frontotemporal dementia – with behavioural ones. In diagnosing dementia the most important are an interview, laboratory, neuropsychological, CT and MRI investigations. In AD treatment cholinesterase inhibitors are most often used while in VaD – antiarteriosclerotic drugs and those improving cerebral circulation. Long-lasting rehabilitation is playing an increasingly significant role in treating these groups of patients.

Słowa kluczowe
choroba Alzheimera, otępienie czołowo-skroniowe, otępienie naczyniopochodne, otępienie z ciałami Lewy'ego, farmakoterapia, rehabilitacja

Streszczenie
Otępienie jest zaburzeniem wyższych funkcji korowych często występującym w starości, spowodowanym chorobą Alzheimera (AD), otępieniami: naczyniowym (VaD), z ciałami Lewy´ego lub czołowo-skroniowym. Etiologia AD jest nadal nieznana. Najważniejszymi czynnikami predysponującym są: gen APOE 4, wiek, płeć, krótki okres edukacji, zawód nie wymagający aktywności umysłowej i występowania otępienia w rodzinie. Główne zmiany patomorfologiczne polegają na obecności w mózgu płytek starczych oraz zwyrodnienia włókienkowego, a patofizjologiczne na zaburzeniu w układzie cholinergicznym. AD objawia się podstępnym początkiem, powolnym przebiegiem, zaburzeniami pamięci, orientacji i zachowania, afazją, apraksją, agnozją, przestawieniem rytmu dobowego snu, trudnościami w ubieraniu i utrzymywaniu higieny. Później występują halucynacje, urojenia, nietrzymanie zwieraczy, postępujące osłabienie, którego skutkiem jest leżący tryb życia, dołączają się infekcje i odleżyny. VaD spowodowane jest najczęściej niedokrwieniem. Do czynników ryzyka tego otępienia należą głównie: wiek, płeć, nadciśnienie, niski poziom wykształcenia, nikotynizm, cukrzyca, hipercholesterolemia. W VaD częściej niż w AD obserwuje się nagły początek, skokowy przebieg, zachowany krytycyzm, obniżony nastrój. Występuje częściej u mężczyzn. Otępienie z ciałami Lewy'ego przebiega z nasilonymi zaburzeniami pozapiramidowymi, natomiast czołowo-skroniowe z zaburzeniami behawioralnymi. W diagnostyce otępień najważniejsze są: wywiad, badania laboratoryjne, neuropsychologiczne oraz CT lub MRI w celu wykluczenia innych przyczyn zaburzeń. W leczeniu AD stosuje się głównie inhibitory acetylocholinesterazy, a w VaD leki poprawiające krążenie mózgowe oraz przeciwmiażdżycowe. Coraz ważniejszą rolę odgrywa długotrwały proces rehabilitacji.

Definition

According to the World Health Organisation, dementia (lat. *dementia*) is defined as a syndrome induced by cerebral disease, usually chronic or progressive, characterised clinically by numerous disturbances of cortical cognitive functions such as memory, thought, orientation, comprehension,

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counting, learning ability, language and judgement. The above cognitive functions disturbances are frequently accompanied or even preceded by emotional, behavioural and motivational disturbances.

Prevalence

The prevalence of dementia increases with age from less than 1% in the age range of 60–64 years to almost 40% at the age of over 90 years, and the index of this process doubles every 5.1 years. The prevalence of dementia in the whole geriatric population ranges approx. 2–10%[1,2].

A study on dementia in Poland conducted in the Warsaw population determined its prevalence as 5.7% in people aged 65–84 years[3]. In the population of villages and little towns, the prevalence of dementia was 3.5% for Alzheimer's disease (AD) and 3.6% for vascular dementia (VaD)[4]. During the late senility (75 years and older), dementia was suspected in 23.6% of persons in the city population and in 17.8% in the village population, more frequently in women[5].

The most frequent cause of dementia in the western societies is Alzheimer's disease constituting approx. 50–70% of all cases of this syndrome. Its prevalence is estimated for 1.9 to 5.8% in the geriatric population[1]. The majority of reports indicate its increasing incidence in women. Prevalence of AD doubles above 65 years of age every 4.5 year[6], and the age is considered the best established risk factor for this disease.

Vascular dementia is the second most frequent dementia type after AD in the European and North American countries (with a prevalence of 12–30%), and the most frequent in some Far East populations (India, Japan, China, Russia). Its prevalence doubles every 5.3 years[7,8].

The true prevalence of the fronto-temporal dementia (FTD) has not been precisely determined. Currently, it is assumed that in the elderly, it is the fourth most frequent, and in the younger people even the second most frequent cause of dementia after AD[9].

Dementia with Lewy bodies (DLB), rarely diagnosed clinically, constitutes, according to some neuropathological studies, as much as 7–34% of all dementia syndromes[10].

Types of dementia

Alzheimer's disease

The most frequent primary degenerative disease of the brain leading to dementia was described in 1906 by a German neurologist, Alois Alzheimer. Precise data on the prevalence of this disease in Poland are unavailable. According to various sources, at least 250000 – 400000 people suffer from this disease, which indicates that in each average family physician's area, there are approx. 30 persons with AD. A significant number of cases of the disease are undiagnosed and untreated or treated inappropriately[10].

A biological factor, the apolipoprotein E gene (the APOE 4 gene) localised to the chromosome 19, referred to as "susceptibility gene" (8-fold increased risk of the disease) is considered to be the most important factor predisposing to AD. In cases of the presence of two ε4 alleles (APOE4/4), the disease occurs earlier and progresses more rapidly, when there is one ε4 allele – the progression is slower. Apolipoprotein E is present in the senile plaques, neurones and amyloid deposits, participates in their aggregation, and regulates the density of synapses.

Mutations of the β-amyloid precursor protein (APP) gene (chromosome 21), the presenilin I gene (chromosome 14) and the presenilin II gene (chromosome 1) play an important role in the pathology of dementia in some patients (10–15% of AD cases)[11,12].

The following features are also considered to be important risk factors for AD: age, sex (the disease is more frequent in women), short education period, jobs not requiring mental activity, family history of dementia syndromes, head trauma. Recently, an important role of cardiovascular risk factors in AD aetiology has been noticed[12].

Presence of two changes in the cerebral tissue is considered to be the basis for pathological diagnosis of AD: senile plaques and neurofibrillary tangles. Senile plaques are extracellular changes of approximately 20–150 microns size being primarily β-amyloid deposits – a protein of a 39–43 amino acid-chain, formed from the amyloid precursor protein with the participation of secretases. The plaques occur in various forms of "maturity", they are built up of a centrally located amyloid core surrounded by microglia and astroglia. They contain presenilin I and II, apolipoprotein E (ApoE) produced by the astrocytes and macrophages. Amyloid, via its toxic effects on the neurones, induces slowing of axonal transport and disturbances of phosphorylation of another protein typical for AD – the tau protein, which in turn contributes to the formation of the other change characteristic for this disease – neurofibrillary tangles. In the ultrastructural evaluation, this degeneration has a form of paired helical filaments comprising in 80% the excessively phosphorylated tau protein (normally, one molecule of this protein contains 2–3 phosphate groups, in Alzheimer's disease – 8–10). Hyperphosphorylation induces changes in the structure of microtubules, which subsequently contribute to greater hydrophilic properties of the cytoplasm and neuronal damage. This pathology can also occur in other neurodegenerative diseases; however, most frequently accompanies AD, and the number of changes correlates with clinical symptoms and a reduction in the number of neurones[11,12]. Less specific changes are also observed in the brains of patients with dementia of Alzheimer-type, such as: diffuse amyloid deposits in the walls of cerebral arteries, neuronal reduction, reduction in the number of synapses, increased microglia and astroglia reactivity and diffuse white matter changes.

Disturbance of cholinergic transmission with a reduction in cholinergic neurones number and in choline acetyltransferase activity with concomitant increase in cholinesterase activity (the enzyme decomposing acetylcholine) are considered to be most important in the pathophysiology of Alzheimer's disease. Apo E exerts a significant effect on the function and integrity of the cholinergic system. In the pathophysiology of AD,

disturbances of other neurotransmitters (serotonergic, dopaminergic, glutamatergic) are also emphasised.

In the last years, the role of the disturbed lipid metabolism, via the ApoE – the main lipoprotein of the central nervous system – in the pathophysiology of dementia of this type has been denoted. Increased cholesterol level induces acceleration of β-amyloid aggregation and hyperphosphorylation of the tau protein[13].

Insidious onset, slow progression (faster in younger patients), disturbances of memory – originally recent, then also remote, aphasia, orientation and behavioural disturbances are typical for Alzheimer's disease. At the beginning, decreased mood, rarer – depression, with preserved criticism can occur; in the later course of the disease, dysphoria, increased mood, sometimes jocular attitude or mania associated with anxiety, lack of concentration and compulsive walking are more frequent[12]. Sleep disturbances are usually present in the later stage of the disease. Reversal of the circadian rhythm with drowsiness during the day and arousal during the night (sunset syndrome) is typical. Permanent signs of the disease also include: apraxia, agnosia, difficulties in dressing-up and maintenance of personal hygiene. In the advanced stage of the disease, sphincter dysfunction, hallucinations, delusions, worsening of gait, progressive weakness, stiffening of the trunk with aggravation of extrapyramidal signs occur. In the terminal phase of the disease, patients are unable to move independently, later even despite assistance. As a consequence of this state, patients remain in bed, muscle atrophy and limb contractures occur, decubitus, urinary and respiratory tract infections appear. The latter three complications constitute the most frequent causes of death in patients with AD dementia[11,12].

For the staging of Alzheimer's disease, the GDS (Global Deterioration Scale according to Reisberg – table 1) is often used in a clinical setting[14]. It is a seven-point scale of patient's functioning based partially on the history taken from the family and caregivers and on the examination of the patient. In the first stage of the disease according to the GDS, no cognitive decline is present (pre-clinical phase), in the second – only very mild disturbances of recent memory are present, depression and conflicts with patient's environment can occur. In the third period – of mild cognitive impairment – loss of the ability to work and of full, independent functioning in the environment (inability to cope with money-related issues, to safely drive, to use phonebook and plan trips and shopping) occur. In the next stage (mild dementia), there are disturbances of orientation in time and space, hygienic negligence, loss of sensation of risk and emotional irritability and instability. In the fifth phase of the disease (moderate dementia), difficulties in sphincter control occur, compulsive walking and behavioural perseverations are present. In the next stage (moderately severe dementia), further disturbances add to the clinical picture: difficulties in motion (falls, shuffling gait, holding on to the household facilities, difficulties in gait initiation and standing-up), eating with fingers, aggravated speech disturbances (word perseverations, limited vocabulary, difficulties in speech comprehension, sometimes echolalia) and delusions. In the terminal stage of the disease (severe dementia), the abilities of communication and locomotion are lost; there is a complete dependence on the caregiver (necessity of feeding); uncontrolled behaviours (e.g. persistent cry) and neurological signs (parkinsonism, frontal release signs, convulsions can occur) are present as well as complications add to the clinical picture.

It is assumed that the average duration of the disease, starting with the time of its diagnosis, is approx. 8–14 years. In clinical practice, diagnosis of the disease is made no earlier than in the third or fourth stage, which corresponds to a shorter disease course, of approximately 5–7 years.

The Mini Mental State Examination (MMSE) is most frequently used as a screening test for dementia[15].

For the diagnosis of the type and degree of dementia, it is necessary, apart from the history and physical examination, to perform laboratory studies (basic tests, thyroid gland hormones, vitamin B12) to exclude other (mainly internal diseases-associated) causes of cognitive function disturbances (anaemia, especially associated with B12 deficiency, hypothyroidism, respiratory, heart, renal and hepatic failure-associated encephalopathies, electrolyte disturbances, hypoglycaemia, chronic drugs and alcohol abuse). Neuropsychological and neurological evaluation must be taken into account for the diagnosis of AD, as well as CT and MRI studies must be performed to rule out causes of dementia other than AD (tumours, stroke, subdural haematoma, normotensive hydrocephalus). In the AD evaluation (but not in common clinical practice), positron emission tomography, cerebrospinal fluid examination (with β-amyloid and tau protein assay), assessment of the apolipoprotein E gene polymorphism are also used[11,12].

Dementia is most commonly diagnosed according to the criteria of the American Psychiatric Society – the DSM IV[11,12]. Memory disturbances

Table 1

Global Deterioration Scale – GDS[14]

	Level	Symptoms
1.	No cognitive decline	disease diagnosed accidentally
2.	Very mild cognitive decline	disturbances of recent memory
3.	Mild cognitive impairment	getting lost in travel, difficulties in shopping
4.	Mild dementia	disturbances in orientation in time and space
5.	Moderate dementia	non-independent in self-service
6.	Moderately severe dementia	incontinence, delusional behaviours
7.	Severe dementia	loss of speech, loss of psychomotor abilities, e.g. of gait, immobilisation in bed, complications

and presence of at least one of the following cognitive disturbances: aphasia, apraxia, agnosia, executive functions disturbances, constitute the basis of the diagnosis. The listed cognitive dysfunctions elicit significant difficulties in the social or professional life and there is a decrease in the level of functioning in comparison to the level previously observed in the patient. For the diagnosis of AD according to these criteria, it is also necessary to rule out other causes of cognitive dysfunction. Other criteria, according to the ICD–10, also consider disturbances duration longer than 6 months as a factor increasing the probability of AD diagnosis.

When establishing the diagnosis of Alzheimer's disease, other above mentioned causes of cognitive disturbances as well as depression and acute disturbances of consciousness (delirium) should be excluded. The most important features differentiating Alzheimer's disease from vascular dementia include: progressive course in AD, without somatic complaints, absence of pronounced neurological signs and focal changes in the CT scans. Women suffer from AD four times more frequently than men.

Vascular dementia

This disease primarily refers to men and is characterised by a stepwise progression, with presence of somatic complaints and neurological signs. In CT scans, focal changes in the brain are observed[11,12]. This form of dementia occurs most often as a result of ischaemic, less frequently haemorrhagic or inflammatory, changes. Multi-infarct dementia (cortical) is the most frequent form of vascular dementia. Much rarer, vascular dementia may manifest as subcortical dementia (Binswanger's disease) or dementia associated with a strategic stroke (localised in the thalami, in the base of the forebrain, in the caudate nuclei or in the angular gyrus of the dominant hemisphere). Clinically, cases of mixed forms of various VaD types as well as their coexistence with AD are frequently observed[16].

The features considered to be the most important risk factors for VaD include age, male sex, low educational level, vascular risk factors for atherosclerosis: arterial hypertension, nicotine smoking, previous myocardial infarctions, diabetes mellitus, hypercholesterolemia, as well as increased homocysteine level and presence of antiphospholipid antibodies. Prevalence of vascular dementia after cerebral stroke ranges from 9.2% to 56.3%[16].

Fronto-temporal dementia

This form of dementia is a neurodegenerative process in the brain with dominant behavioural disturbances and personality change (the frontal variant) or, less frequently, with speech disturbances (the temporal variant). Principal symptoms of FTD include: slow onset and progressive course, early occurrence of social behavioural disturbances, absent self-criticism and presence of emotional dullness. The following features confirm the diagnosis: behavioural and speech disturbances, frontal release signs, bradykinesia, tremor and muscle rigidity, neuropsychological evaluation demonstrating frontal deficits with the absence of profound memory disturbances. Neuroimaging studies reveal atrophy of the frontal lobes and/or of the anterior parts of the temporal lobes. There is a family history in approximately 30–50% of cases. In the clinical praxis, this dementia is rarely diagnosed, most frequently as a form of AD[9].

Dementia with Lewy bodies

This type of dementia is associated with psychopathological disturbances (psychotic syndromes and behavioural disturbances), with accompanying dizziness, falls and parkinsonian features. It is three times more frequent in men. For the diagnosis of probable DLB, two symptoms and for the possible DLB, one of the following symptoms is required:

- fluctuations of cognitive dysfunction with particularly pronounced attention disturbances,
- recurring visual hallucinations that are clear and detailed,
- parkinsonian signs.

The diagnosis of DLB is favoured by: recurrent falls, syncope, transient consciousness disturbances, hypersensitivity to neuroleptics, systematic delusions and hallucinations[17,18].

In the differential diagnosis of AD with depression, establishing the diagnosis of AD is favoured by: insidious onset, progressive course, recent memory disturbances, night-time worsening, labile mood, absent criticism. Conversely, the onset of depression is usually acute, the course non-progressive, disturbances of recent and remote memory are similar, aggravation of symptoms occurs in the morning, the mood is stabile and the criticism preserved[19].

Delirium

Delirium (lat. *delirium*) is an acute cerebral syndrome manifested as impairment of the brain function and cognitive dysfunction induced by dehydration, electrolyte disturbances, hypoxia, hypoglycaemia, intoxication (particularly with drugs). Therefore, the time criterion is crucial for the differential diagnosis of dementia. Possible causes of delirium in the elderly may include almost all somatic and psychiatric diseases, a change in the environment, stress, drugs, dehydration and alcohol. The most frequent symptoms of delirium are acute disturbances of consciousness, concentration, orientation in time and space, psychomotor agitation, perception disturbances, impairment of abstract thinking, illusions and hallucinations, most frequently visual[19].

Treatment and rehabilitation

As cholinergic system disturbances are the early and important biochemical change in Alzheimer's disease, use of cholinesterase inhibitors has been most justifiable in the pharmacotherapy of AD[20]. There are currently three drug substances authorised for marketing in Poland: donepezil (Aricept, Yasnal, Donepex, Cogiton), rivastigmine (Exelon) and galantamine (Reminyl).

In the last years, memantine (Ebixa, Axura) – a low affinity antagonist of NMDA receptors inhibiting the excessive glutamatergic system activity observed particularly in the advanced stage of Alzheimer's disease – has been introduced to the treatment of

this disease. Neuroprotective agents (piracetam, selegiline – a MAO-B inhibitor, antioxidants – Vit. C, E, B6, trimetazidine), preparations improving cerebral circulation (nicergoline, vinpocetine, pentoxyphyllin, gingko biloba extract) are also used in the therapy (although their efficacy in AD has not been univocally proven). Of the above preparations, mainly selegiline and vitamin E are worth attention, because the disease progression modulating effect was demonstrated for these agents in a large randomised study[21]. However, there is no explicit evidence for the effectiveness of adding vitamin E to cholinesterase inhibitors in AD therapy. Results on the efficacy of treatment of cognitive deficits in Alzheimer's with gingko biloba extract preparations are also contradictory.

In the advanced dementia, patients primarily require treatment of agitation and sleep disturbances (neuroleptics are most often used), although currently, there is also an opinion that at this stage of the disease, cholinesterase inhibitors may be also effective, as they not only improve cognitive function, but also have positive effects on behavioural disturbances in AD[20,22].

In VaD management, primary and secondary prevention of atherosclerosis is most important. Use of preparations improving cerebral blood flow has not been unequivocally proven to have beneficial therapeutic effects. Use of cholinesterase inhibitors may also be justified in VaD, as cholinergic deficit is also present in this disease[16].

The therapy of fronto-temporal dementia primarily involves symptomatic treatment. In many cases, selective serotonin reuptake inhibitors may be useful because of the reduction of serotonergic transmission, and in cases of agitation and aggression – neuroleptics may be administered[9].

Dementia with Lewy bodies is symptomatically treated with cholinesterase inhibitors and levodopa preparations. Hypersensitivity to neuroleptics and paradoxical reaction to benzodiazepines in this form of dementia should be born in mind[22].

Apart from the pharmacotherapy, non-pharmacological methods play an important role in the treatment of dementias. They aim at preservation of the activity and independent self-service, training memory and orientation, reducing stress and improving quality of life. Education of the caregivers and formation of support groups in home-care and in day-care centres are particularly emphasised[23].

At each stage of the disease, physical rehabilitation, adjusted to actual patient's abilities, improving physical agility and intellectual skills (also by influencing cerebral blood flow) and reducing emotional tension and anxiety is recommended[24]. Appropriately selected exercises for the patients with dementia ensure maintenance of good physical fitness by reinforcing muscle strength, increasing bone mass, counteracting balance disturbances and preventing falls. Moreover, mild tiredness following physical effort facilitates falling asleep and improves sleep quality. Physical exercises also stimulate intestinal motility thus preventing chronic constipation. They also alleviate and reduce the frequency of such symptoms as anxiety, agitation and wandering. Finally, performance of the exercises by the patient together with his caregiver favours maintaining the contact between them and diminishes the intensity of anxiety and depression symptoms in the patient[24].

In each phase of the disease, the aim of the rehabilitation is to take maximum advantage of patient's potential abilities of self-service, to maintain independent functioning skills still not disturbed in the deterioration process (including hand exercises enabling independent eating and dressing-up, exercises of the pelvic muscles in order to maintain sphincter control), to prevent falls, immobilisation in bed and aggravation of extrapyramidal disturbances resulting both from dementia itself and from undesirable effects of the drugs (neuroleptics). Finally, in the terminal stage of the disease, the goal of rehabilitation involves prevention of complications, primarily of decubitus and infections.

In the studies by Arkin[25], cognitive functions deterioration was not observed during a 20-week observation, despite the progressive character of the disease, in any of the AD patients, in whom physical exercises (short warm-up, stretching exercises, treadmill and cycloergometer training, exercises with weights as well as a 20-minute walk) were conducted regularly twice a week. A noticeable improvement of general physical agility and mood was observed. In Andersen's[26] observations, increasing the activity of every-day living also ameliorated dementia patients' quality of life.

Meta-analysis of 30 studies on the significance of physical rehabilitation in patients with dementia (a total of 2020 patients above 65 years of age) explicitly proves that individually adjusted physical exercise programme improves cognitive function and has beneficial effects on behavioural disturbances at each stage of the disease[27].

In dementia, other non-pharmacological forms of therapy are also recommended, such as: memory training, singing, music therapy, therapeutic fine arts and dancing. The aim of these activities is to improve functioning of memory, orientation in time and space and patient's quality of daily living. Recently, a significant role of the so-called reminiscence therapy in dementia has been emphasised, which involves evoking reminiscences using stimulating materials (objects, sounds, paintings, pictures, smells – the so-called memory anchors). Some centres for AD patients therapy offer "rooms of reminiscences" arranged like typical flats as of before several decades, where, in a therapeutic group, patients are provoked to recall and share their memories. It was demonstrated that this form of therapy alleviates behavioural disturbances as well as has a better effect on patients' activity and general feeling as compared to the standard programme of simple exercises[28].

Appropriately conducted, comprehensive, pharmacological and non-pharmacological therapy, adjusted to actual clinical status, where it is important to avoid hyperprotectiveness and changes in environment (including unjustified hospitalisations), plays a key role in the management of a patient with dementia.

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