

Comorbidities disorders and Alzheimer's disease

Zaburzenia i schorzenia współistniejące z chorobą Alzheimerą

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Abstract

Introduction. Alzheimer's disease is a chronic, progressive, neurodegenerative disease of the brain initially runs with disorders of higher cortical function, leading to dementia and a complete failure. Among the most important modifiable risk factors stand out: advanced age, genetic predisposition towards dementia and sex. Ch Orob Alzheimer's disease is heterogeneous in terms of clinical, neuropathological, biochemical and molecular level, can take place accompanied by a number of disorders and disease entities.

Purpose. Presentation and discussion of disorders, and comorbidity of Alzheimer's disease.

Materials and methods. Using a key Alzheimer's disease (*Alzheimer's disease*), comorbidities (*comorbidity*) Polish and foreign searched electronic bibliographic databases: *Polish Medical Bibliography, EBSCO Host Web, Wiley Online Library, Springer Link, Science Direct, Medline.*

Results. Finally, analysis of the scientific reports showed that frequently co-existing disorders, and Alzheimer's disease include: disease entities associated with hypoestrogenemia, cognitive and behavioral deficits, depression, diabetes type 2, conversion of ocular disorders and eating habits, sleep, bladder control bladder and bowel, and sexual dysfunction.

Conclusions. A multitude of sickness characterized by Alzheimer's disease shows coercion interdisciplinary care for early diagnosis not only cognitive deficits but also often concomitant ophthalmic internal medicine, neurological and psychiatric disorders.

Key words: Alzheimer's disease, comorbidities, risk factors, epidemiology.

Streszczenie

Wstęp. Choroba Alzheimera to przewlekła, postępująca, pierwotnie neurodegeneracyjna choroba mózgu przebiegająca z zaburzeniami wyższych czynności korowych, prowadząca do otępienia i pełnej niesprawności. Wśród niemodyfikowalnych najważniejszych czynników ryzyka wyróżnia się: zaawansowany wiek, uwarunkowania genetyczne w kierunku otępienia oraz płeć. Choroba Alzheimera jest schorzeniem heterogennym pod względem klinicznym, neuropatologicznym, biochemicznym i molekularnym, może przebiegać w towarzystwie licznych zaburzeń oraz jednostek chorobowych.

Cel. Przedstawienie i omówienie zaburzeń oraz schorzeń współistniejących z chorobą Alzheimera.

Materiał i metody. Posługując się kluczowymi chorobą Alzheimera (*Alzheimer's disease*), choroby współistniejące (*comorbidity*) przeszukano polskie oraz zagraniczne elektroniczne bazy bibliograficzne: *Polska Bibliografia Lekarska, EBSCO host Web, Wiley Online Library, Springer Link, Science Direct, Medline*.

Wyniki. Ostatecznie analiza doniesień naukowych wykazała, że do często współistniejących z chorobą Alzheimera zaburzeń oraz schorzeń można zaliczyć: jednostki chorobowe związane z hipostrogenizmem, deficyty poznawcze i behawioralne, depresję, cukrzyce typu 2, zamiany oczne, a także zaburzenia nawyków żywieniowych, snu, kontroli nad pęcherzem moczowym i jelitami oraz zaburzenia seksualne.

Wnioski. Mnogość chorobowa charakteryzująca chorobę Alzheimera ukazuje przymus opieki interdyscyplinarnej w celu wczesnego zdiagnozowania nie tylko deficytów poznawczych ale również często współistniejących okulistycznych, internistycznych, neurologicznych i psychiatrycznych zaburzeń.

Słowa klucze: choroba Alzheimera, choroby współistniejące, czynniki ryzyka, epidemiologia.

Introduction.

In the early twentieth century German neurologist Alois Alzheimer described the clinical and histopathological changes that occur in dementia with no known cause in 51 year old woman. A close associate of Alzheimer's - Emil Kraepelin in the eighth edition of *Psychiatrie* in 1910 introduced the medical term "Alzheimer's disease" and recognized it as a subtype of senile dementia [1, 2].

Alzheimer's disease (Alzheimer's disease - AD) is a chronic, progressive, degenerative originally (neurodegenerative) extending from a brain disease activity higher cortical dysfunction such

as memory, cognitive, and affective behavior, leading to dementia and complete failure that prevents the proper functioning of the patient in everyday life [3,4,5]. The most important risk factors include age. The incidence of AD before the age of 65 does not exceed 1% at age 65 years, however, it rises sharply to 5-10% and up to 30-40% of the tower and toward 85lat above. The mean duration of symptoms with fatal outcome of 10 years [6,8].

According to scientific reports female gender is also an important risk or nnik.AD occurs three times more often in women than in men. Initially it was thought that women often suffer from dementing disease because they live longer, but most studies show a greater incidence of women than men, even when standardized age of both groups [10].

On the occurrence of AD also have considerable influence genetic factors. Currently, it is considered the most significant occurrence of mutations in three genes: the gene for amyloid precursor protein (APP) on chromosome 21, presenilin 1 on chromosome 14 and the presenilin 2 on chromosome 1The emergence of these mutations determines the occurrence of Alzheimer's disease is an autosomal dominant inherit usually early onset of symptoms (early-onset AD, EOAD).In the case of an inherited form of AD symptoms may appear even in the three decade of life. In the late onset AD, ie after 65 years of age (AD late-onset, LOAD) gene mutations are associated apolipoprotein E (APOE).APOE polymorphism on chromosome 19 is the normally occurring variations of the gene, which is likely to substantially increase susceptibility to AD. In some families with late-onset AD and APP mutations and in patients with Down's syndrome, each APOE allele can influence the reduction in the age of onset of dementia. The presence of additional genetic material in individuals with Down's syndrome that survive to the age of 50-60 increases the susceptibility of those with AD, AD therefore occurs more frequently in the population than in the general population [6,7,8,9,11]. It is worth noting that the genotype is more useful to predict when this may lead to the development of the disease, than whether or not the individual will develop AD. The mere presence of a gene predisposing no diagnostic value, but increases the specificity of the diagnosis of AD [11].

Purpose. Presentation and discussion of disorders, and comorbidity of Alzheimer's disease.

Materials and methods. Using a key Alzheimer's disease (*Alzheimer's disease*), comorbidities (*comorbidity*) searched Polish and foreign full-text electronic bibliographic databases: *Polish Medical Bibliography, EBSCO Host Web, Wiley Online Library, Springer Link, Science Direct, Medline.*

Results and Discussion.

Hormonal disorders and Alzheimer's disease

You may ask yourself why it is the female gender is predisposed to a higher incidence of this disease? It must be remembered that all the structures and functions of the brain are estrogenosensitive. Estrogens have an effect on neurotransmitters and neurons. Also exhibit neuroprotective bioenergetic system regulate brain glucose metabolism and oxidative phosphorylation processes have an effect on glucose transport substrates [12,14]. It follows that estrogen deficiency leads to a state of the brain hypometabolic crisis. Reducing the level of glucose metabolism causes use of other sources of energy as lipids, which favors the development of AD. The sharp decline in

estrogen levels observed in postmenopausal women. Thus, the diseases that coexist with AD may include all conditions associated with expiration of ovarian hormonal activity and consequently amended hormonal profile occurring in postmenopausal women [13,14,15]. During menopause, many women report symptoms that have not occurred. The main problems in this period include:

1. The ordered power exceeds the available capacity of the WTTP. This makes it necessary to limit the area under consideration and to supply a part of it from the EDF west main. Abnormal uterine bleeding of various types with the most common form of arrhythmia menstruation [16,17];
- 2 Complaints from the urogenital - vaginal dryness, inflammation of the vagina, dyspareunia, recurrent urinary tract infections, lower and genital prolapse, urinary incontinence, libido disorder [16,18];
- 3 Postmenopausal changes in tissue-thinning of the skin, reducing the activity of the sebaceous glands and sweat glands, hair loss, bone and joint pain [16,19];
4. Osteoporosis and osteopenia - due to an imbalance between bone resorption and bone opening process is a reduction of bone mass, which in turn leads to increased risk of pathological fractures [16,20];
5. Metabolic disorders - such as dyslipidemia, serum menopausal women is increasing concentrations of total cholesterol, triglycerides, LDL cholesterol and Lp (a), on the other hand, lowering HDL cholesterol, impaired glucose tolerance to insulin, hyperinsulinaemia, type 2 diabetes [16,21];
- Obesity - peri - post-menopausal and distribution of a change of body fat. Excess body fat in the network and the abdominal subcutaneous tissue, which in turn increases the considerable ie atherosclerosis [16,22];
- 7 Cardiovascular disease - atherosclerosis, coronary heart disease, hypertension, venous thromboembolism [16,23];
8. Neoplasms - menopausal women increases the incidence of cancer. The most common are sequentially cancer breast cancer, lung cancer, cervical cancer, stomach cancer, ovarian cancer, endometrial cancer [16,24].

All the above. disease entities associated with hypoestrogenemia can coexist with progressive dementia characteristic of Alzheimer's disease, so be sure of an interdisciplinary approach to patient doctor with AD.

Cognitive impairment and behavioral and Alzheimer's disease

AD is characterized by a slow and gradual deterioration of memory and other cognitive functions. In most cases, the initially observed subtle memory disorder known as mild cognitive impairment-MCI (mild cognitive impairment).In confirmation of MCI plays an important role intelligence collected from those closest to the patient and the deterioration in tests to assess individual functions, standardized according to the age and level of education. MCI does not significantly affect daily functioning. In time, join others mainly cortical symptoms such as aphasia, usually mixed, apraxia, agnosia, and impairment of executive functions.

In addition to cognitive impairment in the course of AD is often observed behavioral disturbances such as wandering and aimless wandering (pacing), states verbal and physical aggression, apathy and social withdrawal (including sexual), neglect of the teams hallucinational-delusional (disambiguational-delusional, delusional stealing, marital infidelity, misidentification), abnormal rhythm sleep [25].

Depression and Alzheimer's disease

Many studies show that even in 90% of patients, especially in the early phase of the disease are mental disorders, mainly in the form of depressive syndromes and anxiety [26]. An analysis of the research also shows that more than half of the patients have episodes of depression throughout their lives au third depression manifests clinically during dementia [27]. Depression can be the first symptom of AD. Epidemiological data suggest that mood disorders often accompanied by mild to moderate forms of the disease [28]. The etiology and pathophysiology of depression in AD is not fully understood. Attention is drawn to the relationship of gene polymorphism associated with brain neurotransmitter systems, e.g. with serotonergic, dopaminergic, and the genes associated with the development of the brain [29]. Sweet et al studies have observed a correlation between a polymorphism in the range of insertion / deletion of a long-allele of the serotonin transporter promoter (5-HTTPR) and the appearance of symptoms of psychotic and aggressive behavior [30].

Also ongoing research on the participation of neurotrophins in the pathogenesis of cognitive impairment and mental AD. They Attention is mainly on account of brain-derived neurotrophic factor (BDNF), a potent modulator of synaptic transmission and its activity is associated with the processes of learning and memory [31,32]. AD patients showed reduced levels of BDNF in the temporal cortex and parietal [33]. In autopsy studies of patients with concomitant depression noradrenergic neuronal loss demonstrated within the locus coeruleus in the brain [34]. As risk factors for depression in AD are distinguished: mood disorders, affective disorders occurring in first-degree relatives, the occurrence of an episode of depression before the diagnosis of AD, early onset AD, and female gender [35]. Research conducted by Agnieszka Jatzak-Stanczyk et al suggest that depression in AD occurs with profound cognitive dysfunction and indicate a lack of relationship between the efficiency of cognitive function and age and education as well as their severity greater in women than in men suffering from depression course of AD [36].

Other authors also point to the possibility of pseudo dementiaonal depression, which affects most areas of cognitive, psychomotor slowing in particular, disorientation, attention, memory and recall, information processing and language functions. Depressed mood may increase the loss of concentration, changes in behavior and response [37]. It was also demonstrated less severe depression in AD patients than in a control group without any signs of AD. Much more frequent in subjects with AD depression accompanied by psychotic symptoms as hallucinations and delusions which may be related to elevated levels of dopamine in the region of the hippocampus [38]. Approximately 10% of patients with AD in the late stage of the disease develops Capgras syndrome-patients are convinced that their loved ones or caring for them were turned by the scammers [39].

Type 2 diabetes and Alzheimer's disease

Type 2 diabetes and AD in light of recent research should not be viewed as two completely separate disease entities. It is extremely important epidemiological reasons. According to the latest International Diabetes Federation (IDF) diabetes in the world in 2013, 382 million people suffered and it is estimated that by 2035, this issue touches 592 million people. The vast majority of cases of type 2 diabetes is Studies show that the risk of the development of AD is approximately 2.5 times higher in people with diabetes type 2 [41-45]. Currently, much research is focused on answering the question of whether AD is a disorder of glucose metabolism in the central nervous system, diabetes or Alzheimer's is a disease of the pancreas [40].

It is proposed that consideration of both diseases as amyloidosis. The pathogenesis of both AD and type 2 diabetes is involved deposition of amyloid deposits, which include fibrillation of proteins deposits. In diabetes it is the amylin, and AD β -amyloid (A.beta). Not be deemed to have them for specific organ and diseased. The transgenic mouse models of Alzheimer's disease β -amyloid deposits outside the brain were found were abundantly in pancreas and in the kidney. The formation of conglomerates fibrils cause cytotoxic reactions in their formation causing damage. In its wake comes to the death of cells and their replacement by amyloid. These reactions are common to A.beta and amylin and lead to the development of both diseases. There is even a hypothesis suggests considering AD as diabetes type 3 diabetes or selectively affecting the brain [40,42,44-50].

Studies also show that cerebral glucose metabolism in patients with AD is impaired. This is due to the loss of glucose transporters. Patients who have developed Alzheimer's disease show a reduced expression of GLUT1 and GLUT3 especially in the cerebral cortex, with significant loss of GLUT3. This is confirmed by studies using PET showing reduced glucose transport most metabolically active regions such as the cerebral cortex, hippocampus brain microvessels isolated [45,52,53].

Another hypothesis was put forward on the basis of tests on models of AD transgenic mice. It suggests that reduced regulation of insulin receptor substrate gene may be conducive to the transition event changes associated with age changes characteristic of Alzheimer's disease tangent [51].

An important effect of coexistence of these diseases is that the occurrence of type 2 diabetes in patients suffering from AD significantly increases the risk of a functional failure. In addition to diabetes, it represents a weakening balance, obesity and adopting multiple drugs. Diabetes increases the risk of neuropathy, at the same time increases the risk of imbalances of one leg, and thus increases the possibility of the collapse of such a person. [54] Also, brain imaging studies show a link between diabetes and changes in the nature of brain atrophy, sinus attacks and loss of white matter [55,56].

In conclusion, given the epidemiological data and the relationship of these two diseases in the future they can be a serious problem in geriatric practice.

Ocular disorders and Alzheimer's disease

Based on the latest reports, began to debate the ocular variant of AD. This is the form in which the ocular symptoms predominate that appear first. For their occurrence may correspond to the deposition of β -amyloid deposits and their toxic effects on the eye and occipital parts of the brain. Freight to the disappearance of the retinal ganglion cells. In addition to the havoc made by the interaction of amyloid plaques, are responsible for the symptoms of ocular disorders also probably the

concentration of neurotransmitters, particularly acetylcholine and disorders of the trail glutaminergic [48,50,57-62].

In patients suffering from Alzheimer's disease can expect more frequent than in the AD population nonconverters such changes occur glaucoma, pseudoexfoliative (Pseudoexfoliation syndrome - PEX), macular degeneration, age (Age-related Macular Degeneration - AMD), Dyschromatopsia, impaired sharpness vision for distance, cataracts, decreased contrast sensitivity [57, 58, 60, 62, 63, 67]. In the group of patients with AD have a much higher risk of developing glaucoma. It is possibly associated with increased intraocular pressure, and lower resistance fibers of the optic nerve caused by accumulation of amyloid β -nicotinamide in the structures of the eyeball [57,58,62,63]. Pseudoexfoliation syndrome (pseudoexfoliation) is the accumulation of deposits in a number of pathological organs include anterior ocular tissue of the lung, kidney, cardiac muscle, blood vessels, skin, liver, urinary bladder, gall bladder and meninges. This syndrome is one of the risk factors for glaucoma, open-angle glaucoma. The collected material outside exfoliation core surrounded by a protein glycosaminoglycans found to contain β -amyloid [57, 58, 64, 65, 66]. Many studies have confirmed more often by about 1.5-2 times the occurrence of AMD in individuals suffering from Alzheimer's disease. In the course of AMD reaches the β -amyloid deposition in the retinal pigment epithelium [57]. According to the literature disturbances in visual acuity in patients suffering from AD may favor the occurrence of visual hallucinations. That is why it is so important for the management of these patients, visual acuity testing especially since these patients have an increased frequency reduced her visual acuity for distance [57,67,68]. Uncharacteristic color vision disorders affect mostly blue and green with sparing of the red color. They can result either from the decreased level of melatonin in patients with AD or from changes in the visual cortex due to the underlying disease. Perhaps there is also overlap between these phenomena [57,58].

There have also been reports about the possibility of early diagnosis of ocular lesions associated with AD using electrophysiological tests. Studies have been conducted visual evoked potentials. In the examined groups of patients had a bioelectrical dysfunction of the optic nerve and retina. Noteworthy deviation of an extension of the latency of P100 (study PVEP), prolonged latency of wave P50 (study PERG) and prolonged latency wave P2 (Study FVEP). Longer is also time-cortical retinal. They demonstrate the ganglion cell damage and optic nerve, and photoreceptors and bipolar cells suppository. These studies suggest the possibility of early diagnosis of AD [59].

Abnormal eating habits and Alzheimer's disease

Changing eating habits can be the first symptom of developing dementia. Some patients may eat too much, too fast, do not know when they are replete. They can often simply forget that he ate the meal, they may repeatedly ask for another portion, which will entail an increase in body weight [69, 70]. Unfortunately, in the later stages of chewing and swallowing instincts may be lost, and this is due to the development of dysphagia pseudobulbar [71]. Dementia is a common the cause of weight loss [72, 73]. Nearly twice as many AD subjects experienced a weight loss of 5% or more as compared with the control group in the study by White H et al [69]. Some patients first see the protein-energy malnutrition exacerbated later. The continuous progression of dementia causes deterioration of sense of taste and smell by the patients, which in combination with the excessive activity (alternating movements, agitation, aggression) causes an imbalance between consumption and wear [71]. In

patients contributes to the development of agnosia, causing difficulty in recognizing things edible and using cutlery. Additional factors that influence weight loss is a disease accompanying depression, attention deficit disorder (difficulty concentrating on more than one element of a meal) or difficulty with self-eating [71, 74, 75]. Weight loss may also result from disturbances of vision, and more specifically with reduced sensitivity to contrasts of color [75], which is often observed in advanced stages of the disease. As a result, patients may have difficulty in distinguishing e.g. on the content of blood or blood from the table.

Ensuring good nutrition in AD can be a challenge, but it's worth it. Good nutrition can help patients cope better - both physically and emotionally - with the challenges of AD.

Sleep disorders and Alzheimer's disease

In patients observed abnormal sleep-wake cycle, causing daytime sleepiness and accompanying sleeplessness at night. Often these patients are hours like minutes, may confuse day and night, and vice versa [74,76]. The causes of this phenomenon is seen in the frequent wakes up the during sleep, reduced sleep efficiency, increasing the proportion of sleep phases 1 and shortened sleep phase 3 [71]. Are also important changes in the pattern of REM sleep [76]. In addition, lack of physical activity during the day, frequent naps, caffeine intake, untreated, pain and frequent use of the toilet at night causes frequent getting up at night [74]. Patients in the evening or night are symptoms of the setting sun [77]. In the afternoon or evening the older person has a grudge, it becomes argumentative, spiteful, does not want to listen to reproaches, accused, sometimes aggressive. In the evening, the blood pressure drops, the brain reaches less oxygen and glucose, plus accompanying dehydration, revealed a drop in mood, worsening confusion and / or agitation [74].

Disorders of bladder control and bowel and Alzheimer's disease

The loss of control over bowel and bladder is common in the later stages of AD. At the beginning of this problem can occur sporadically or during sleep. The occurrence of urinary incontinence in a patient with mild dementia strongly suggests complication commonly associated with infection of the respiratory tract. Urinary incontinence can be caused by many factors, including the inability to recognize the need to use the toilet, forgetting where the bathroom and how to use the toilet. In addition, medications, stress, certain physical conditions and the difficulty in undressing contribute to these problems. Often associated with constipation also worsen control of her bladder. Patients with dementia are not able to remember the proper way of defecation (eg they may urinate in a rack or basket, or simply do not know what to do when they get to the bathroom). [74] If the cause of urinary incontinence is treatable, we should seek to regain control of micturition and defecation by the patient.

Sexual dysfunction and Alzheimer's disease

In some cases, people with AD may exhibit excessive sexual activity, which may manifest itself in words or deeds of individuals to others. People with forget about the rules that govern sexual behavior in public places, to the extent that they can undress and masturbate in front of others [74].

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Please note that this behavior is the result of changes in the brain, not the loss of moral principles by patients.

Conclusions

From the above article it is clear that for patients suffering from Alzheimer's disease should be holistic approach not focusing on only on cognitive impairment, as a leading symptoms. Please seek other disorders of the fields of ophthalmology, internal medicine, neurology and psychiatry to improve the quality of life of these people. It is also important as early diagnosis, which may indicate a developing disease process associated amyloid deposition.

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