Psychiatr. Pol. 2022; 56(5): 991–1001
PL ISSN 0033-2674 (PRINT), ISSN 2391-5854 (ONLINE)
www.psychiatriapolska.pl
DOI: https://doi.org/10.12740/PP/150052

Cardiovascular factors in dementia

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Summary

Dementia affects a significant portion of the population of elderly people and thus has become one of the most important health problems. At the same time, people with dementia are more likely to be also affected by concomitant diseases. Cardiovascular factors seem to be of particular importance. It has been shown that problems regarding blood pressure as well as lipid and carbohydrate metabolism play a crucial role for the rate of cognitive deterioration in elderly individuals in both vascular cognitive impairments and primary degenerative impairments (e.g., Alzheimer's disease). A clear relationship is observed between vascular pathology and degenerative processes in the brain. The period of life in which the exposure to cardiovascular factors occurs seems to be key, and these relationships are best documented in middle age. With aging, their importance as factors accelerating the progression of cognitive impairments seems to diminish, especially in Alzheimer-type dementia. Research on the importance of comorbidity in dementia processes may be crucial for the development of prevention and therapy programs for dementia.

Key words: dementia, risk factors

Introduction

Alongside the increasing average age of the population, the prevalence of different forms of dementia is increasing. Nowadays, this constitutes a significant socioeconomic problem, being a burden not only for healthcare systems but also, in particular, for the caregivers of affected individuals. Dementia is usually preceded by a period of decreased cognitive function, which can last for variable lengths of time [1–3]. The rate of increase of cognitive impairments depends on many factors. These include age, family history [4, 5] and the presence of certain genetic factors, such as the ε4 allele of apolipoprotein [6]. However, none of these factors can be modified through interventions. Therefore, efforts should focus on identifying factors that can potentially be modified and which accelerate the process of cognitive deterioration. According to the *Lancet Commission on Dementia Prevention, Intervention and Care,* as many

as 35% of all cases of dementia are significantly susceptible to interventions aimed at modifying risk factors [7].

The processes leading to the histopathological changes underlying dementia begin many years – if not decades – before the clinical onset of a disorder [8]. Introducing preventive measures in old age might be too late. It is believed that no more than 5% of individuals with dementia have an identifiable genetic predisposition – all others seem to suffer from so-called sporadic forms of dementia, whose roots lie in a wide variety of pathogenic factors [9]. For most part, these factors can be modified, which could be of significant importance for preventing further progression of cognitive impairment.

The occurrence of other conditions, not directly concerning the central nervous system, used to be an overlooked element of the pathogenesis of dementia processes [10]. In reality, individuals with dementia are much more likely to also suffer from other conditions [11]. The presence of other conditions impacts the course of dementia in a multitude of ways. They negatively impact the functioning of a patient and decrease the chances of successful therapy. Moreover, they may be related to the pathogenetic mechanisms which underlie dementia processes [12]. Some studies have suggested that the presence of concomitant conditions is associated with greater progression of cognitive impairment [10]. Epidemiological studies have reported relationships between cognitive deterioration and arterial hypertension, diabetes and hyperlipidemia. This is the case for types of dementia whose primary causes are associated with both vascular processes and degenerative processes (e.g., Alzheimer's disease) [13–16]. Cardiovascular factors are not the only ones that matter for the progression of cognitive impairment – conditions of the respiratory system, the liver (cirrhosis) and kidneys can also play a role [17]. However, most research has been devoted to studying risk factors associated with cardiovascular diseases, and thus these are the ones we know relatively more about. Several vascular mechanisms have been proposed to play a role in accelerating degeneration. One of the hypotheses proposes that due to the weakening of the blood–brain barrier in aging individuals and previous immunization of the system (e.g., due to injuries to the skull), immunological reactions occur that result in damage to brain cells. It is a fact that the number of damaged small vessels correlates with amyloid plaques in the cerebral cortex [18].

Arterial hypertension

The relationship between arterial hypertension and faster progression of cognitive impairment is often mentioned. It is suggested that every reduction of 10 mm hg of either systolic or diastolic pressure is associated with a significant decrease in the risk of dementia [19]. Moreover, treatment with diuretic agents may reduce the risk of the development of dementia [20]. The relationship between arterial hypertension and the progression of cognitive impairment is most visible if the most dominant symptoms during the period before the clinical onset of dementia concern cognitive functions other than memory (e.g., executive functions, thinking, attention) [21].

However, not all studies support such a relationship. A body of research did not find an association between dementia and hypertension; a few publications even re-

ported that increased blood pressure was a factor reducing the risk of development of dementia [22, 23]. Meta-analyses of research contributed greatly to the explanation of the aforementioned discrepancies. Empirical data support the claim that treatment for hypertension results in decreased severity of dementia; however, the period of life in which such interventions happen is of key importance [24]. While such a relationship exists for individuals who are about 50 years old, continuing hypertension treatment later in life may be associated with increased risk of dementia [25]. Naturally, receiving the treatment itself may be associated with varying circumstances and does not necessarily lead to a lasting decrease in blood pressure. However, based on studies which directly monitor blood pressure, it appears to be the case that while hypertension in middle-aged individuals (about 50 years old) is a risk factor for dementia, moderately increased blood pressure functions as a protective factor in elderly individuals [26, 27]. Incidentally, a similar relationship exists with relation to the problem of being overweight: it is a risk factor for middle-aged individuals, but in the elderly it is associated with a better prognosis [28]. According to some data, a few years before the clinical onset of dementia, the blood pressure already begins to decrease [29]. The moderately increased blood pressure in elderly individuals does not play this proposed protective role in every type of dementia – it pertains only to the group of so-called primarily degenerative dementias, especially Alzheimer's disease and Lewy body dementia. Arterial hypertension remains a risk factor throughout the entire lifespan for vascular dementia [17].

It should also be noted that ascribing a protective role to higher blood pressure (i.e., above the norm) in the elderly is not widely accepted. The belief that there is no significant association between dementia and hypertension, hyperlipidemia, or diabetes in elderly people seems to be more grounded in empirical data [17]. This picture is different for decreased blood pressure, especially in periods directly preceding the onset of dementia. Already many years ago, big epidemiological studies suggested considering low blood pressure a risk factor for dementia, including primary degenerative dementia [30].

Diabetes

A relationship between impairment in carbohydrate metabolism and faster progression to dementia has been widely reported. It is especially visible in individuals who already present some, usually mild, memory impairments. The presence of diabetes and the amnesiac form of mild cognitive impairment is associated with an increase in conversion to dementia, especially Alzheimer-type dementia [31, 32]. On the other hand, later studies suggest that even an increase of fasting blood glucose itself (especially above 100 mg/dl) in individuals with mild cognitive impairment is a risk factor for conversion to dementia, especially Alzheimer-type dementia [34]. Observations made in recent years support the existence of a pronounced relationship between the presence of diabetes and faster progression of cognitive impairment in individuals in whom mild cognitive impairment is already present [10]. It is emphasized that the mechanisms involved in the acceleration of degenerative processes are complex [13,

34]. The possible association with neurodegenerative processes may be indicated by the proposed role of insulin in the growth of nervous cells, the functioning of glial cells, the maintenance of energetic homeostasis of the brain, oxidative stress, as well as the modulation of inflammatory processes in the central nervous system [35, 36]. The role of insulin in the maintenance of the integrity of the blood-brain barrier might be key: some scholars propose that the impairment of this barrier is associated with the onset of the so-called amyloid cascade through the initiation of inflammatory processes in the brain [12].

Hyperlipidemia

Epidemiological studies suggest that increased levels of cholesterol are another factor increasing the risk of the development of dementia, especially Alzheimer-type dementia. Another argument is also the decrease of the prevalence of dementia in individuals who take medication to lower blood cholesterol [31, 37], which has not been replicated [38]. Nonetheless, it is a fact that most studies have reported a relationship between blood cholesterol levels and the risk of dementia, especially Alzheimer-type dementia. However, there also exist reports to the contrary or which indicate that the increased risk for dementia is related to decreased cholesterol levels [39].

As in the case of hypertension, it appears to be that the period of life examined by a given study may be key here. The relationship between increased cholesterol levels and the risk of the occurrence of sporadic (not genetically determined) types of dementia pertains to middle age [40]. This association seems so significant that, nowadays, when constructing algorithms for calculating the risk for Alzheimer's disease and other types of dementia, levels of cholesterol and HDL fraction in middle age are taken into account [41]. Similar relationships are noted also for vascular dementia. Increased levels of cholesterol in middle age are associated with increased risk of dementia in old age [42]. On the other hand, the results of studies concerning later periods in life vary significantly. Some report a relationship between increased levels of cholesterol and lower risk of dementia, some did not report any association, and some reported opposite results [43]. There are more uniform results regarding the HDL cholesterol fraction – higher values of which are associated with lower risk of vascular dementia [38]. The proper assessment of results regarding cholesterol is a complex task. Apart from there being many relevant factors (usually not controlled in studies) that can influence one's metabolism, it should be taken into account that levels of cholesterol generally decrease with age [44]. Age may also be associated with changes in dietary choices and all forms of activity, which can also be reflected in the metabolism of lipids. For example, a prospective study on a large population sample in Denmark, which took into account not just lipid profiles but also levels of physical activity, age and the presence of other psychopathological symptoms (mainly depressive symptoms), did not report an association between higher cholesterol levels and risk of dementia [45].

It is a fact that cholesterol plays an important role in the functioning of the central nervous system. It is believed that about a quarter of the cholesterol in the human body

is contained in the brain. Cholesterol is the main ingredient of the lipid membranes of brain cells. It is present in neurons, glial cells, as well as myelin sheaths and thus plays a crucial role in the process of synaptic transmission [46]. Cognitive deficits are believed to be associated with decreased synaptic transmission, which may be associated with impairments in the biosynthesis of cholesterol. Moreover, a decrease in cholesterol inhibits the growth of dendritic spines, lowering the intercellular integration [47]. The relationship between levels of lipids and vascular dementia is better documented. Decreased blood supply to the brain is associated with higher levels of LDL and lower levels of HDL, which is also associated with higher risk for coronary disease and carotid artery disease [38].

When discussing the proposed associations between lipids and dementia, it is worth noting that the E4 isoform of apolipoprotein E (ApoE) – a known risk factor for Alzheimer's disease – is a precursor of the protein engaged in the transport of cholesterol in the brain. At the same time, it directly binds with chains of Aβ proteins, influencing their aggregation and removal [48]. Moreover, cholesterol is proposed to play a role in determining the activity of beta and gamma secretases – the enzymes responsible for fragmentation of the amyloid precursor protein (APP). The solubility of the produced Aβ fragments depends on the activity of these enzymes [38]. In the next stages, the increased production of insoluble Aβ fragments causes the increase of histopathological changes that occur in diseases such as Alzheimer's disease. Having the E4 isoform is associated with higher levels of serum total cholesterol and LDL fraction, which is a risk factor for arteriosclerosis.

In the context of the problem of lipid metabolism, one should also mention the proposed importance of statins for the progression of cognitive impairment. The results of some epidemiological studies from the early twentieth century seemed to suggest that statins played a protective role. However, an increasing number of studies seem to contradict this. A meta-analysis of studies on over 26,000 patients aged about 40 with cardiovascular risk factors did not support the notion that using statins decreased the level of risk for dementia or slowed down the progression of cognitive impairment [38]. The conclusions presented by Bettermann et al. [49] are quite convincing: they suggested that statins may be a protective factor, but only for individuals with no cognitive impairment. A positive effect is not observed even in the case of small cognitive impairment [48, 49]. These conclusions are not only consistent with earlier epidemiological studies, but are also in line with the observations about many other factors (e.g., regarding the composition of one's diet) which may have an effect if the exposure happens much earlier than the onset of the dementia processes [50]. The use of statins in elderly people does not have an effect on the progression of cognitive impairments, both in the case of processes that are primarily degenerative and vascular [37].

For a complete picture, it is also worth mentioning reports suggesting the negative impact of statins on cognitive functions [51, 52]. These reports were treated so seriously that the US Food and Drug Administration issued a warning accordingly [37]. A clear limitation of most studies on statins is treating them as a homogenous group. The compounds pharmaceutically and clinically defined as statins differ in their chemical composition. This means that their potential impact on cognitive function

may vary, and they may impact cognitive functions in ways other than just through the regulation of levels of lipids.

The cardiovascular factors comprise only one of the many groups of potentially modifiable risk factors for dementia, but they are the most documented. This is owing to long observation studies with large groups of participants, such as, for instance, the Framingham Heart Study [53]. The primary goal of these studies was to assess cardiovascular problems, but they also provided valuable data for improving our knowledge of psychopathology. Owing to such research programs, the importance of cardiovascular factors in the pathogenesis of dementia is now considered indisputable. Vascular changes – both peripheral and in the central nervous system – are closely related to the risk of developing dementia [43]. This applies to all kinds of dementia, not just, as it may seem, vascular dementia. Cerebral infarction lesions (usually minute) are a frequent element of the radiological picture of Alzheimer's disease [54–56]. Histopathologically, in almost half of all individuals diagnosed with Alzheimer's disease, there is the presence of not only amyloid in senile plaques and neurofibrillary bundles, but also vascular changes (e.g., infarction lesions). It has been shown that the presence of subcortical infarction lesions with concomitant amyloid pathology increases cognitive deficits and increases the prevalence of dementia [43]. All types of vascular damage decrease the threshold of the so-called cognitive reserve, thereby increasing the risk of developing dementia. A few studies have shown that individuals with vascular pathology in the brain present clinical symptoms of dementia already when the changes related to Alzheimer's disease (senile plaques and neurofibrillary bundles) are relatively small [57].

A strong relationship has been observed between Alzheimer's and vascular pathology. One example of this is that the accumulation of Aβ in the middle layer of small brain arteries weakens vascular walls, thereby increasing the probability of bleeding [58]. Moreover, the presence of Aβ in vascular walls impairs blood supply and cerebrovascular autoregulation [59]. All this, together with the increase of tension in the vascular muscles, leads to the reduction in cerebral blood flow observed in Alzheimer's disease [60]. The presence of Aβ deposits, especially in the perforating arteries of the brain, is common in Alzheimer's disease and is observed in 80–100% of brains of people with Alzheimer's disease that undergo autopsy [61].

The assessment of the significance of risk factors for dementia is difficult because of its polyetiologic character. Analyzing factors individually seems to be of dubious merit. A more appropriate direction seems to be to analyze as many factors as possible together [62]. The age at which the importance of given factors is assessed is crucial. Obesity, as well as the previously-discussed hypertension, hypercholesterolemia and hyperglycemia, are documented risk factors for the development of dementia; however, this only pertains to middle-aged people. With further aging, their importance as risk factors that accelerate the progression of cognitive impairments seems to diminish [14, 30].

The beginning of the process of dementia is not univocal in its clinical manifestation. First, histopathological changes, e.g., neurofibrillary bundles, appear in the structure of the hippocampus years or even decades before the clinical manifestation

of, for example, Alzheimer's disease [2]. The hippocampus is one of the key structures responsible for the regulation of levels of glucose, fat deposits and, generally, the metabolic rates [63]. Neurodegenerative processes damaging the hippocampal structures and other centers in the brain lead to impaired regulation of the body's metabolism, which may lead to further development of brain dysfunction [64]. Moreover, it is very likely that, in at least some cases, the same mechanisms underlie both the changes in the brain and peripheral changes. An example worth highlighting is the previously-mentioned ε4 allele of apolipoprotein E, which is associated with an increased risk of cardiovascular diseases [57] and is a known risk factor for Alzheimer's disease [6].

The existence of a relationship between the cardiovascular system and mental condition was first suggested a long time ago. Recently, more and more attention has been paid to its importance for risk of cognitive impairments. The clinical manifestation of dementia is preceded by neurobiological processes that take years, and that can be modified by a number of factors at every stage of development. The level of progression of cognitive impairment depends on the severity of cardiovascular factors. Preventive measures and treatment at early stages of life may contribute to limiting dementia-related problems in old age.

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