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Hypertension and dementia – A brief overview

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ABSTRACT

Introduction: As the population ages, the prevalence of neurodegenerative diseases, including dementia, is expected to grow substantially. These diseases have a poor prognosis, yet early treatment may significantly slow down their progress and, in particular, prevent patients from deteriorating into advanced stages of dementia. Although chronic arterial hypertension is an established risk factor for dementia, the relationship between hypertension and Alzheimer's disease, the most common cause of age-related dementia, has not been fully clarified.

Aim: The aim is a brief overview of current knowledge about the relationship between hypertension and dementia with a focus on Alzheimer's disease.

Methodology: A review of information and current scientific knowledge about the relationship between hypertension and dementia was carried out.

Findings: Scientific evidence suggests that hypertension plays a key role in cognitive decline, Alzheimer's disease, and vascular dementia. The relationship between blood pressure and cognitive function is, however, complex and is not yet completely understood. Age is considered to be the most important factor influencing the role hypertension plays in the development of dementia. Other factors are insulin resistance, menopause, inflammation, and the APOE-ε4 genotype. The mechanism of these interactions remains unclear. So does the relationship between hypertension and Alzheimer's disease, the monitoring of which is complicated by multiple factors.

Conclusions: Hypertension in this regard is a possible modifiable risk factor, which may be crucial to preventing or delaying age-related cognitive impairment. Understanding the relationship between hypertension and dementia is thus a research priority.

KEY WORDS

Hypertension, Dementia, Alzheimer's disease

LITERATURE OVERVIEW QUESTION

The latest results of studies identifying hypertension as a possible modifiable risk factor that may play an important role in the prevention of dementia, point to the following question: What is the current state of knowledge about the relationship between hypertension and dementia with a focus on Alzheimer's disease as the most common cause of age-related dementia?

BACKGROUND

The 21st century is referred to as the century of degenerative and in particular, neurodegenerative diseases. The prevalence of these diseases, including dementia, is estimated to increase substantially and rapidly as the population ages (1). Vascular dementia, which is age-related and is most often caused by Alzheimer's disease (AD) or cerebrovascular factors, is thus becoming the main threat to public health. Although chronic arterial hypertension is an established risk factor for both types of dementia, the relationship between hypertension and its treatment and cognition has not been fully clarified to date (2).

DESCRIPTION OF THE RESEARCH STRATEGY

The paper is a literature review aimed at providing a brief overview of current knowledge about the relationship between hypertension and dementia with a focus on Alzheimer's disease. Relevant literature was

searched using citation indexes such as Web of Science, SCOPUS, and Google Scholar. The search used mostly the combinations of the keywords "hypertension" or "blood pressure" and "cognitive function" or "dementia" or "Alzheimer's disease". The greatest importance was attached to the results of epidemiological meta-analyzes, systematic reviews, and studies from the period 2010–2020.

LITERATURE OVERVIEW

Epidemiology of Dementia

Dementia is a disorder where the patient suffers a significant loss of memory and other cognitive functions. It is accompanied by a loss of memory, intellect, and the ability to communicate, including the gradual loss of habits and skills. (1). Dementia is one of the most common neurological disorders worldwide, affecting an estimated 40 million people. It is assumed that the number of individuals with dementia will have tripled by 2050, mainly due to population ageing (2, 3, 4). Dementia affects about 5% of population aged 65, and its prevalence doubles with every five year increase in age (3). The number of people with dementia living in the Czech Republic in 2016 was estimated at 155,900. This is the estimated number of people with dementia; the actual figures are unavailable. At the same time, dementia is often misdiagnosed.Alzheimer's disease International reports that only about half of the population is diagnosed with dementia even in the most advanced countries (4).

Alzheimer's disease and cerebrovascular disease are major causes of cognitive impairment, accounting for about 80-90% (of which AD alone constitutes 60%) of all cases, although often it is a mix of both pathologies (1, 5). Alzheimer's disease is, in short, the most common form of dementia, with a prevalence of 1% of the population. It is the fourth to fifth most common cause of death. Despite its poor prognosis, early treatment can significantly slow AD and, more importantly, prevent the patient from deteriorating into advanced stages of dementia. Causal therapy is currently not available (6).

Alzheimer's disease

Alzheimer's disease is a severely progressive and irreversible neurodegenerative disease. It typically starts as a subtle, creepy process; the first symptoms are noted by family and friends rather than the patient themselves. The clinical picture shows cortical degeneration, characterized by an imprinting capacity disorder with lapses of recent memory. Early stages of the disease are marked by discreet emotion changes such as anxiety, irritability, depression, and apathy. Non-cognitive functions are gradually also impaired (6).

Multiple hypotheses have been proposed to explain AD aetiology, the first being the amyloid hypothesis. It suggests that the neurodegenerative changes are triggered by abnormal cleavage of the amyloid precursor protein molecule by beta and gamma secretases. The resulting beta amyloid accumulates extracellularly as microscopic senile plaques. The senile plaques, together with intracellular neurofibrillary tangles, which are formed by hyperphosphorylated tau protein, cause a loss of neuronal function and reduce the number of neural synapses, leading to neuronal death. At the macroscopic level, cortical atrophy initially presents in the medial temporal lobe and associated cortical areas and later in the entire brain. In accordance with the above findings, cerebrospinal fluid analysis was added to the AD diagnostic criteria (7, 8). Cerebrovascular disease is not part of AD diagnosis for research purposes (8, 9); it is vascular dementia. The symptoms of AD and cerebrovascular disease, however, often present side by side. This disease is referred to as mixed dementia and lacks clear diagnostic criteria. Interestingly, patients meeting the AD diagnostic criteria are more likely to have vascular symptoms and risks compared to the cognitively intact population. These findings have prompted alternative hypotheses, according to which the vascular hypothesis of AD is the cause of the neurodegenerative process of vascular changes (7).

Epidemiology of hypertension

Arterial hypertension is a serious health problem in developed countries. According to a 2014 study by the European Health Examination Survey (EHES) (10), the prevalence of hypertension in the Czech Republic (CR) was found for the younger group aged 25 to 44 years to be 19% (14% of women and 26% of men; $p < 0.001$), while among the elderly, aged 45 to 64 years, the prevalence was 54% (44% women and 69% men; $p < 0.001$) (11). Approximately 40% of hypertensive men and 24% of hypertensive women are unaware of their disease. Effective management of hypertension, namely achieving target blood pressure (BP), is recorded in approximately 47% of treated men and 66% of treated women (10).

Arterial hypertension is a repeated increase in BP ≥ 140/90 mm Hg measured at a minimum of two different visits. The following three stages of hypertension are defined:

- Stage I (mild hypertension) with BP 140–159 / 90–99 mm Hg,
- Stage II (moderate hypertension) with BP 160–179 / 100–109 mm Hg,
- Stage III (severe hypertension) with BP ≥ 180/110 mm Hg.

Hypertension is further classified according to which BP value is elevated as: systolic-diastolic hypertension, isolated systolic hypertension (particularly common in elderly patients), and isolated diastolic hypertension (12).

Hypertension as a risk factor for cognitive decline

Hypertension is a significant risk factor for cardiovascular and cerebrovascular diseases. Scientific evidence suggests that hypertension plays a key role in cognitive decline, AD, and vascular dementia (13).

The harmful effect of hypertension on cognitive function was identified as early as the 1960s, when reduced psychomotor speed was discovered in hypertensive air traffic controllers and pilots compared to those without hypertension (14).

Understanding of the relationship between cardiovascular dysfunction and brain health has improved significantly over the last few decades, yet it remains unclear whether hypertension is a potentially treatable / modifiable risk factor for cognitive decline and dementia. Although it is evident that hypertension may affect brain structure and function, recent findings suggest that the relationship between blood pressure and brain health is more complex and in many cases depends on other factors such as age, chronicity of hypertension, and antihypertensive use (13).

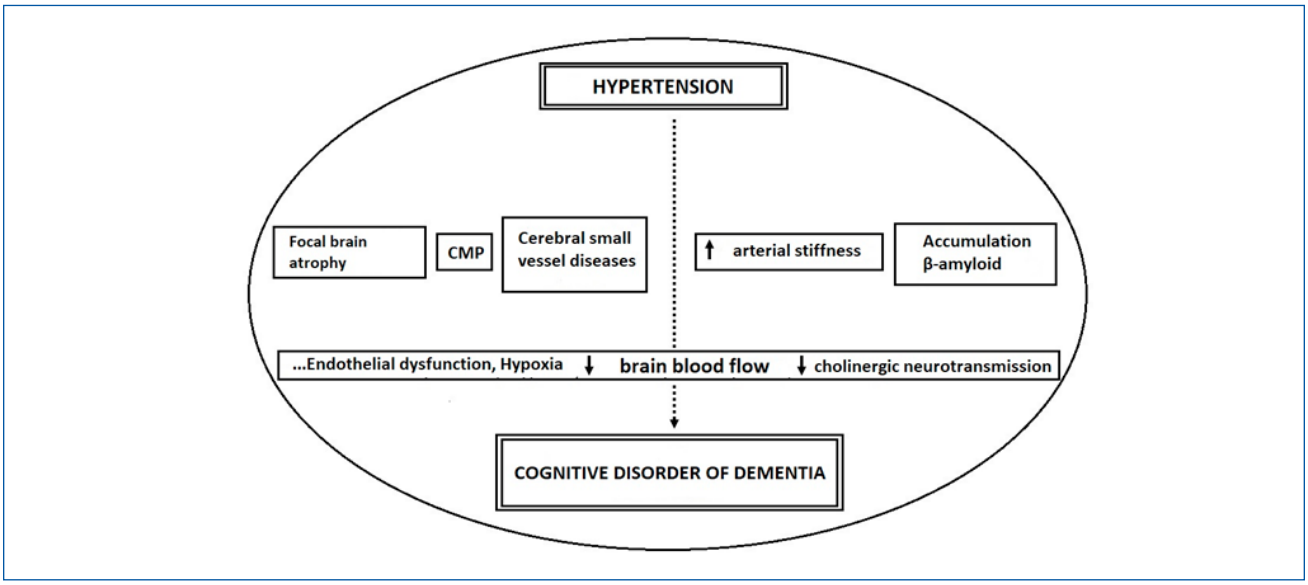
Mechanism of the relationship between hypertension and cognitive impairment / Dementia

Hypertension is assumed to predispose to early cognitive impairment, which develops into dementia and stroke over a time interval which can last several months to years. While most patients with hypertension remain asymptomatic during this time, elevated blood pressure predisposes to the development of minor changes due to narrowing arterioles or microvascular changes, which lead to chronic focal or diffuse ischemia of small vessels (lacunar infarct or white matter lesions) and hemosiderin deposits in perivascular spaces, particularly deep *a. perforantes* (micro-bleeding) (15). Figure 1 shows the possible mechanism of the relationship between hypertension and cognitive impairment/dementia. Table 1 shows the possible mechanisms linking increased blood pressure to the risk of cerebrovascular disease (including cognitive impairment).

Table 1 Possible mechanisms linking increased blood pressure to the risk of cerebrovascular disease (including cognitive impairment) (15)

Oxidative stress
Alteration of endothelial function
Inflammation
Nocturnal BP decrease (dipping) or non-dipping
Altered renin-angiotensin system
Increased arterial stiffness
Impaired endothelial progenitor cell function
Increased blood-brain barrier permeability
Decreased beta-amyloid clearance
Arteriolar tortuosity in the white matter
Atrophy of the brain
Cerebral small vessel diseases (white matter lesions, lacunar infarction, microbleeding)
Cerebral amyloid angiopathy

Fig. 1 Possible mechanism of the relationship between hypertension and cognitive impairment/dementia (15)



Factors influencing the role of hypertension in the development of Dementia

Age is the most important factor influencing the role of hypertension in the development of dementia. The risk of impaired cognitive function is increased by hypertension in middle age and low blood pressure in old age. In elderly patients (> 80 years), it is unclear whether the relationship between low BP and cognition impairment reflects dysfunction of the autonomic nervous system with decreased diastolic BP, which in turn leads to hypoperfusion and cerebral atrophy. Further research into this age group, which would take into account the polymorbidity of patients and the propensity for orthostatic hypotension, is needed (2).

While the interaction of male/female gender with hypertension in relation to impact on cognition has not been investigated in detail, a study of a group of 1,034 women (16) suggests an interaction of hypertension with menopause.

Testing cognitive performance in postmenopausal women, it found that hypertensive women scored lower compared with normotensive women, while no such difference was observed among premenopausal women. In further studies, there is growing evidence that the harmful effects of hypertension may be stronger in women compared to men. For example, a study (17) found that although BP was increased more frequently in men, middle-aged hypertension as a dementia risk factor was observed only in women. Hypertension in women aged 40 years was associated with a 65% higher risk of dementia compared to men and a 73% higher risk compared to women who were normotensive in early and middle age. Only a limited number of studies with inconsistent results, nonetheless, have examined possible gender differences in relation to hypertension and the risk of dementia.

Other factors potentiating cognitive impairment in hypertensive individuals are insulin resistance, inflammation, and the APOE-ε4 genotype. The mechanism of these interactions remains unclear (2).

Hypertension and the risk of Alzheimer's disease

Alzheimer's disease, cerebrovascular and cardiovascular diseases share identical genetic factors (18, 19). Approximately 50% of individuals diagnosed with AD have significant cerebrovascular pathology at necropsy (20, 21). These findings suggest that cardiovascular disease, AD, and vascular dementia may have overlapping pathophysiologies (13). Despite evidence for the influence of cardiovascular diseases in the pathogenesis and progression of AD, the relationship between hypertension and AD has not been clarified (13). Based on a meta-analysis (22), earlier observational studies indicate that higher diastolic BP in middle age, not systolic BP, increases the risk of AD. In contrast, higher diastolic BP in older individuals is considered to reduce the risk. According to a recent systematic review and meta-analysis from 2019 based on 4 longitudinal studies (23), a significant association was found between systolic BP > 160 mm Hg and AD (hazard ratio HR 1.25, 95% Cl: 1.06–1.47, p = 0.0065). Similarly, a smaller yet significant association was found for systolic BP> 140 mm Hg (HR 1.18, 95% CI: 1.02–1.35, p = 0.021). No such association was observed for higher diastolic BP. In contrast, a US longitudinal study of 1,259 subjects over 7 years found a relationship between the history of hypertension and an increased risk of vascular dementia (relative risk RR = 1.8, 95% CI 1.0–3.2), yet did not confirm an association with an increased risk for AD (relative risk RR = 0.9, 95% CI 0.7–1.3) (24). These findings are supported by other studies such as the Canadian Study of Health and Aging (25). Other studies reported moderate hypertension to have a protective effect against AD risk in the elderly (2). Still other studies which identified a link between middle-age hypertension and an increased risk of dementia in old age did not compare the risk of AD and vascular dementia (2). An interesting discovery in this respect was made in a Mendelian randomization study. Using a large sample, it found that genetically predisposed high systolic BP was associated with a lower risk of AD (odds ratio OR = 0.75, 95% CI 0.62–0.91 ; p = 3.4 × 10−3). Genetically predisposed higher systolic BP was also associated with a higher likelihood of antihypertensive use (26). The conclusions are complicated by the findings of several other studies, based on which antihypertensive treatment may reduce the risk of AD (27). The studies suggest that methods which effectively reduce BP in middle age, such as lifestyle changes or medication, should maintain and improve cognitive function, thereby reducing the risk of AD (27). Based on a meta-analysis of six prospective cohort studies (28) investigating whether specific classes of antihypertensive drugs reduce the risk of dementia, it was found that high BP subjects undergoing any antihypertensive treatment had a lower risk of dementia (HR 0.88, 95% CI: 0.79-0.98; p = 0.019) and Alzheimer's disease (HR 0.84, 95% CI: 0.73–0.97; p = 0.021) compared to subjects without any antihypertensive therapy. At the same time, no significant differences were found between the specific groups of antihypertensives with regard to the risk of dementia. Monitoring the relationship between elevated BP and the risk of clinically diagnosed AD is complicated by various factors. Mul-

tiple epidemiological studies are limited in assessing dementia subtypes due to the fact that, as noted above, the pathophysiology of AD and vascular dementia overlap. For example, individuals with hypertension may be more often diagnosed with vascular or mixed dementia than "pure" AD, and conversely, individuals with hypertension are more likely to show clinical symptoms of dementia associated with AD pathology stage, which may result in an incorrect association of hypertension with AD (2). The results can be also affected, for example, by different methods of measuring blood pressure and treating hypertension.

RESULTS

Hypertension is a modifiable risk factor, which is a potentially important mechanism in prevention or delay of age-related cognitive dysfunctions. This is why understanding the relationship between hypertension and cognitive decline and dementia is a research priority. The relationship between blood pressure and cognitive function is, however, complex. Although knowledge has advanced substantially thanks to epidemiological studies, the relationship remains unclear. The management of hypertension in terms of prevention and slowing down of cognitive impairments consequently lacks a definitive framework and needs to be further studied.

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