Vascular cognitive impairment and vascular dementia

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Abstract

In the developed world, 5–10 percent of people older than 65 years have dementia. One fifth of dementia aetiologies are due to vascular brain lesions (VaD – vascular dementia). A milder form is called vascular cognitive impairment (VCI). The main clinical criteria for VaD are: 1. cognitive decline verified by standardized cognitive test/scale, 2. evidence of the associated vascular brain lesion, 3. excluded reversible causes of cognitive decline.

The main risk factors for VaD are age, atherosclerosis, diabetes, and hypertension. They play a key role in the pathogenesis of cognitive impairment. Depending on the brain region damaged different cognitive domains can be affected with or without other neurological signs. These diversities in the clinical picture challenge the correct diagnosis. The unique feature of VaD is its progression, which can be stopped, if the patient receives an appropriate treatment.

The treatment of VCI and VaD symptoms is similar to that of Alzheimer's disease. More importantly, VCI may be slowed down or even stopped with proper secondary stroke prevention and good rehabilitation. The most efficient is primary stroke prevention with healthy lifestyle and the treatment of acquired risk factors.

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1. Introduction

Heterogeneous clinical manifestations of cerebral vascular disease (CVD) arise depending on the location of the brain region affected. Beside major physical disabilities caused by vascular lesions in the cerebrum cognitive functions are frequently affected (1). Usually sublime at onset they have been often ignored. In literature, CVD was initially addressed as atherosclerotic dementia and was strictly distinguished from senile dementia (2). Later the terms 'multi-infarct' and 'post-stroke' dementia were introduced; the former describing cognitive impairment after mild recurrent strokes, and the latter after a major symptomatic stroke (2). The term 'vascular dementia' (VaD) was introduced only two decades ago defining the cognitive decline caused by any type of CVD with clinical manifestation of dementia.

Different diagnostic criteria for VaD have been proposed in order to establish the diagnosis more accurately. These criteria have been prepared by the National Institute of Neurological Disorders and Stroke – Canadian Stroke Network Working Group (NINDS-AIREN) (3), Diag-

nostic and Statistical Manual of Mental Disorders (DSM IV-R) (4), International Classification of Diseases (ICD 10), etc. They all define VaD as a cognitive impairment in at least two cognitive domains developed after CVD (6,7). Cognitive function should be independent from other motor-sensory deficits, and should affect the quality of patient's life (6,7).

Nevertheless, milder forms of cognitive decline after CVD remained unclassified. Therefore, similarly to mild cognitive impairment (MCI) in Alzheimer's disease (AD), the term 'vascular cognitive impairment' (VCI) was introduced (8,9). VCI is, in contrast to VaD, defined as a cognitive decline in at least one cognitive domain and does not necessarily affect the quality of life (7,10). The main evaluated cognitive domains are memory, attention, executive function, speech and visuo-spatial processing (6,7,11,12).

Further, Wright and co-workers (7) have divided VCI in four subgroups: amnestic, amnestic with multiple domain impairment, non-amnestic and non-amnestic with multiple domain impairment.

The clinical presentation of VCI and VaD can be either acute, immediately following a symptomatic stroke, developing in stages after recurrent strokes, or subacute with slow progression because of associated neurodegeneration; VCI may gradually improve (13-16).

In this article, we will focus on the main futures of VCI and VaD. We will review epidemiology, aetiology, pathophysiology and main clinical manifestations as well as the methods of prevention, treatment and rehabilitation of this heterogeneous clinical syndrome of growing importance (17,18).

2. Epidemiology

The exact VCI and VaD occurrence is difficult to determine the reason being geographical and ethnical differences of studied populations. Similarly, epidemiological studies are often contradictory due to different research methods (10,16).

The prevalence of dementia in the population aged over 65 years is between 5 and 10 % in developed countries (7,10). Among various aetiologies VaD is the second most common following AD. VaD is responsible for 20 % of dementia cases in developed countries, and for 26 % of dementia cases in undeveloped countries (10,19). There are no data available for the Slovenian population, but a large epidemiological study ILSA carried out in Italy shows that there are 27 % of VaD cases among all dementia cases (20). The incidence of VaD increases exponentially and doubles every 5.3 years, slightly less in comparison to the incidence of AD which doubles every 4.3 years (7,21). Some projections even show that dementias related to vascular pathology will become more common than those of Alzheimer's in the future due to the growing incidence of cardiovascular diseases which are a major risk factor for VaD onset. These are chronic heart failure, atherosclerosis and arterial hypertension (AH) (10). On the other hand, Korczyn and co-workers predict a decline of VaD incidence as the result of better stroke prevention (16).

Furthermore, the prevalence of VCI apparently exceedes that of VaD (7). A recent study has shown that in the USA alone more than 3 million people suffer from VCI (7). Cognitive decline occurs in one third of patients up to three months after a stroke, thereof 8 % develop severe impairment sufficient for the VaD diagnosis (11,22,23). A meta-analysis performed by Makin and co-workers has revealed that VCI develops in 30 % of patients after lacunar stroke, and in 23 % of patients after non-lacunar stroke (24)

larger cortical strokes, except that lacunar strokes are associated with cerebral small vessel disease (SVD. In addition, Douri and co-workers have found that VCI is present in as much as one half of patients 5 years after the stroke (25). Typically, VCI does not deteriorate by itself; however, inappropriate management of underlying causes can progress to VaD. In comparison to correctly managed patients 50 % more of the latter will develop VaD within 5 years (11,16).

The accuracy of epidemiological studies is limited due to divergence of diagnostic criteria for VCI and VaD along with the lack of importance of neuroimaging data which are not regularly attained (16,26). The problem has been pointed out by Prendlebury and co-workers who have found that cognitive impairment is present in 10 % of patients before the first cerebrovascular event (22). In addition, 25 % to 50 % of stroke patients display similar neurodegenerative alterations in brain anatomy as in AD (7).

3. Risk factors

Age is the major and most important natural risk factor for cognitive impairment (10). The incidence of dementia exponentially grows after the age of 50. At the age of 70 and above 10 % of people have dementia, and at the age of 85 and above 20–40 %. In comparison to MCI in AD where the most affected are elderly women, VCI is more common in men younger than 75 (15). It is suggested that education does not have an influence on the onset of cognitive decline by itself, however people with lower level of education have attained poorer results on neuropsychological evaluation (15,16,19).

Furthermore, the races commonly affected by small vessel disease (SVD) are at a higher risk of VCI development. These are Asians, Latin Americans and Afro-Americans (14).

An important finding concerning the risk factors for VaD is their similarity to the risk factors for AD. Therefore, the fact that pathological mechanisms of VaD and AD in comorbid patients often overlap is not surprising (16). This phenomenon is the so-called mixed dementia (27). One of the major acquired factors which increase the risk of VCI and VaD development is atherosclerosis which usually damages large and medium arteries of the circle of Willis (16). An atherosclerotic plaque can rupture, and cause a thromboembolic obstruction of smaller cerebral arteries and brain hypo perfusion (12). Other important cardiovascular risk factors are atrial fibrillation and carotid artery disease (12).

Diabetes mellitus (DM) (12) doubles the risk of dementia development; it increases the incidence of both main types, AD and VaD, yet the patients with DM type 2 are at an increased risk of the latter (28). One brain histopathological study of patients suffering from dementia revealed that non-diabetic patients had higher degrees of Aβ deposits characteristic of AD (29), whereas the brain of diabetics presented more microvascular infarcts, characteristic of VaD (12). Another neuroimaging study showed a clear causal connection between DM, brain atrophy and lacunar infarcts (30): the patients with DM type 1 were at a higher risk of global brain atrophy, whereas the patients with DM type 2 in addition to global brain atrophy had a higher rate of lacunar infarcts (30). In addition, it has been suggested that in diabetics VCI progresses to VaD faster than in patients without DM (31). Additional independent risk factors for dementia are the duration of DM and the associated peripheral artery disease (12,32).

Arterial hypertension (AH) increases the risk of VaD as well (12,33)we investigated the longitudinal relationship of systolic blood pressure, diastolic blood pressure, and pulse pressure with annual progression of WMLs. Means of blood pressure were calculated over a 5-year period before longitudinal MRI scanning. WML progression was subsequently measured on 2 scans 3.5 years apart. We performed analyses with linear regression models and evaluated adjustments for age, sex, cardiovascular risk factors, and baseline WML volume. In addition, we evaluated whether treatment of hypertension is related to less WML progression. Both systolic and diastolic blood pressures were significantly associated with annual WML progression (regression coefficient [95 % confidence interval], 0.08 [0.03; 0.14] mL/y and 0.09 [0.03; 0.15] mL/y per SD increase in systolic and diastolic blood pressure, respectively. It is associated with white matter changes in the brain in the elderly not necessarily suffering from dementia. Nevertheless, uncontrolled AH worsens the natural course of VaD (12,33)we investigated the longitudinal relationship of systolic blood pressure, diastolic blood pressure, and pulse pressure with annual progression of WMLs. Means of blood pressure were calculated over a 5-year period before longitudinal MRI scanning. WML progression was subsequently measured on 2 scans 3.5 years apart. We performed analyses with linear regression models and evaluated adjustments for age, sex, cardiovascular risk factors, and baseline WML volume. In addition, we evaluated whether treatment of hypertension is related to less WML progression. Both systolic and diastolic blood pressures were significantly associated with annual WML progression (regression coefficient [95 % confidence interval], 0.08 [0.03; 0.14] mL/y and 0.09 [0.03; 0.15] mL/y per SD increase in systolic and diastolic blood pressure, respectively. On the other hand, clinical studies show that the appropriate AH treatment decreases the possibility of VaD development (34,35). Early onset AH (about the age of 54) contributes to VaD development later in life (25–30 years later), especially if untreated. It can also cause hippocampal atrophy (12,36–39).

Metabolic syndrome, abdominal obesity, dyslipidaemia, hyperhomocysteinemia, and smoking are indirect risk factors for VaD by triggering cardiovascular diseases.

Depression as a common reflection of chronic illness is typically present in one tenth of the population above 60 years of age (31). Apart from other psychical symptoms it often results in cognitive impairment which should be carefully differentiated from other possible organic aetiologies (40). Half of the patients develop depression within 5 years after a stroke and worsens the disease course (16,41). Moreover, it is a risk factor for VCI (16,41).

Finally, there are a few genetic factors supposedly playing a role in VaD development but their exact function is yet to be elucidated. There are at least two hereditary diseases which increase the risk of VaD, cerebral autosomal dominant (CADASIL) and cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL) (15,16,42,43). Additionally, the genetic mutation of apolipoprotein E ε4 (APOE4), which is responsible for the development of AH and AD, also represents a risk of a stroke and consequent cognitive decline (16).

4. Pathogenesis of VCI and VaD

VCI/VaD develops as a cascade of harmful events triggered by the pres-

ence of risk factors. These lead to CVD which causes hypoxic damage to brain regions involved in cognition (44). Depending on the type of vascular injury VCI/VaD is pathologically divided into large vessel disease dementia, small vessel disease dementia, ischemic dementia and dementia caused by brain hypoperfusion (14).

Thrombosis and thromboembolism of major brain arteries or their branches lead to large vessel disease (14). Total occlusion of the regional brain artery causes the development of large symptomatic brain infarcts which are bigger than 10 mm in diameter (16). 10 % of infarcts are located in brain regions most susceptible to hypoxia, between two regional arteries – marginal zone infarcts (16). Likewise, marginal zone infarcts can develop due to subtotal occlusion of arteries and consequent hypoperfusion of those vulnerable regions (12).

Another characteristic type of brain infarcts associated with VCI/VaD are strategic infarcts responsible for specific syndromes (16). Important strategic regions are angular gyrus, medial frontal cortex, inferior medial side of the temporal lobe, hypocampus and thalamus (13). In multi-infarct dementia, strategic microinfarcts can, apart from cognitive decline, be asymptomatic (12).

SVD is an entity describing damage to brain arterioles, capillaries and venules usually in subcortical brain regions. SVD is the most frequent pathological feature involved in VaD development (14). Apart from genetic background, AH and amyloid angiopathy are the leading causes of SVD (12,45).

Typical pathological changes are seen in vascular endothelium, basal membrane, and smooth muscle layer of arterioles as well as in pericytes. A substantial blood brain barrier (BBB) dysfunction results in damage to the parenchyma of the brain area affected (46). The main pathological features of sporadic subcortical lacunar infarcts are endothelial dysfunction and basal membrane hyalinisation in contrast to cortical lacunar infarcts where amyloid deposition precedes (46). Moreover, a characteristic feature of CADASIL is damage to the smooth muscle layer of arterioles; other hereditary forms of CVD usually involve collagen destruction.

Vascular defects in SVD involve microinfarcts, incomplete infarcts, lacunar infarcts (lacunas, lacunar haemorrhages), expanded perivascular spaces and leukoencephalopathy. The size of lacunar infarct is less than 15 mm, however it can sometimes exceed 20 mm in diameter on axial sections of MRI (47). They are often asymptomatic and can be multiple. Traditionally, the term for multiple lacunas is "*etat lacunaire*" (16). Moreover, incomplete infarcts are associated with ischemic leukoencephalopathy (12).

It should be noted that subdural and subarachnoid haemorrhages as well as the haemorrhage to cerebral parenchyma can all result in VaD (27).

5. Clinical features of VCI and VD

Clinically, a broad spectre of cognitive decline was previously divided into cortical and subcortical dementias. AD was the main representative of cortical dementias with a typical memory loss, whereas post-stroke dementia was considered a subcortical dementia together with dementia in Parkinson's disease. A characteristic feature of subcortical dementia was a decline in executive function (48). However, this concept is somewhat outdated as it is impossible to determine the exact location of pathol-

ogy causing cognitive impairment on the basis of clinical, neuropsychological and neuropathological examinations alone (48).

It is the location and the extent of vascular pathology which determine the neuropsychological profile of VCI/VaD (12,26,45,49). Therefore, in clinical practice it is important to determine a cognitive decline regarding the size of affected blood vessels and the presence of hereditary factors (17,50).

Nonetheless, the out dated division to subcortical and cortical dementias can still be useful regarding the determination of the site of VaD. Smaller subcortical infarcts and leukoencephalopathy lead to subcortical, and major strokes to cortical manifestations of VaD (51) particularly small vessel disease, from those of Alzheimer's disease is a difficult clinical challenge. An influential model of how subcortical cerebrovascular disease causes cognitive dysfunction posits that damage to frontostriatal loops impairs frontal lobe function, leading to predominant impairment of executive function and secondary impairments of associated cognitive functions such as memory. Consistent with this, neuropsychological studies of clinically diagnosed patients have reported that individuals with vascular dementia do better on memory tests and worse on executive function tests compared with patients with Alzheimer's disease. This observation has led to the suggestion that predominant cognitive executive dysfunction might serve as a useful diagnostic marker for vascular dementia. We sought to test this idea in a series of cases with autopsy-defined pathologies. Subjects were 62 autopsied cases from a prospective study of vascular contributions to dementia. Using neuropathological features alone, 23 were diagnosed with Alzheimer's disease (AD.

5.1. Large vascular disease – cortical involvement

Typical characteristics are major hemispheric strokes or strategic strokes which result in sudden onset of symptoms (13,17). Despite indistinct onset and gradual progress, cognitive impairment caused by multiple infarcts also belongs to this group of large vessel disease with cortical damage (17).

The cognitive impairment characteristic of this group is either global, or partial, affecting the memory, visuo-spatial or psychomotor domain.

Regarding the affected brain region, VCI can be accompanied by regionally specific neurological syndromes. Cortical lesions are responsible for the development of paresis, aphasia and apraxia (9,15).

Major strokes to the brain cortex can cause epileptic seizures in addition to cognitive impairment (13,17). One third of the patients with left hemispherical stroke suffer from aphasia (13,17).

Similarly to major strokes, strategic infarcts cause acute onset of dementia (50). Prefrontal cortex is damaged in nearly half of the patients with a strategic infarct resulting in executive function decline (29) manifested as impaired attention and complex planning, disorganised thoughts and altered emotional behaviour, resembling frontotemporal dementia (13,16,21).

Acute memory loss comparable to the clinical presentation of AD is caused by temporal lobe or hippocampal lesions (15,16,52).

Occipital and parietal lobe lesions are associated with impairment of visuo-spatial processing (13). Distinctive is the involvement of gyrus angularis, which, when damaged, causes dysphagia, dysgraphia and visuo-spatial processing dysfunction. Moreover, if the lesion is on

the dominant hemisphere, Gerstmann syndrome develops. Aside from the above mentioned symptoms, it involves acalculia, finger agnosia and left-right disorientation (13).

The main feature of multiple infarcts is impairment of distinct cognitive domains caused by small diffuse ischemic lesions throughout the brain (45). Although the onset is often without clear neurological deficits, unspecific symptoms gradually worsen. It usually starts with urinary dysfunction, gait disturbances and milder forms of cognitive decline (13,17). These signs often resemble those of hydrocephalus. If unrecognised, VCI often worsens and VaD develops (29). Other physical disabilities associated with multiple infarcts are hemiparesis, aphasia, apraxia and agnosia (13).

5.2. Small vessel disease – subcortical involvement

Main clinical features of SVD are syndromes caused by hypothalamic, basal and subcortical frontotemporal lobe impairment (46). Cognitive functions deteriorate gradually. Typical cognitive domains affected are verbal fluency and executive functions (planning, organisation and switching between tasks) (50). In addition, subcortical lesions may cause affective and behavioural disorders (17). These psychical disabilities are usually accompanied by physical ones such as balance and gait disorders and sphincter disturbances (15,16).

The characteristic syndrome with motor control impairment is parkinsonism caused by basal ganglia involvement (12,16). However, there can also be a lesion in the subcortical part of limbic system present resulting in AD-like cognitive decline with preliminary memory impairment.

Apart from clear infarcts there is also brain hypoperfusion which can be responsible for VCI. It should be considered if there is no clear sign of a vascular lesion on neuroimaging (17,50). Its common clinical presentation is global cognitive decline (50).

6. Diagnosis

Many difficulties are involved in the diagnosis of VCI as it has a broad spectre of clinical presentations with distinct cognitive domains affected and severity of impairments (15,16). However, there are three basic criteria that must be met for the VCI/VaD diagnosis: presence of cognitive decline, known CVD and clear chronological relationship between them (21).

These diagnostic criteria for dementia caused by CVD are provided by the Slovenian guidelines issued by the Slovenian Psychiatric Society in 2013 (53), and based on the NINDS-AIREN recommendations. Firstly, the patient must exhibit memory impairment along with at least one other cognitive domain impairment. The cognitive domains to be considered are 1. language, 2. memory and learning, 3. social ability, 4. complex attention, 5. executive functions, 6. sensory-motor functions (54). Furthermore, impairment must be clearly associated with CVD confirmed by neurological examination or neuroimaging. Among positive neuroimaging findings strategic infarct, multiple lacunar infarcts, infarcts in vascular bed of main branches of cerebral arteries or periventricular lesions in the white matter of the brain are listed. Finally, cognitive decline must start immediately or at least within three months after a stroke, whereas in multiple infarcts, cognitive deterioration is gradual.

Dementia caused by CVD is probable if all the above-mentioned criteria are

met. However, if cognition deficits are not so severe to cause patient's dependency or to significantly decrease his quality of life, the diagnosis is cognitive impairment caused by CVD, not dementia.

Nevertheless, it is important to exclude other, reversible causes of cognitive decline and pseudo-dementia (e.g. depression, other mental illnesses) before the VCI/VaD diagnosis is established. Therefore, blood samples should be attained for testing (full blood count, erythrocyte sedimentation rate, biochemical analysis, liver and thyroid function tests, vitamin B12 and folic acid), neuroimaging done as well as other diagnostic tests if needed (electroencephalography, lumbar puncture, positron emission tomography, genetic testing etc.) (6,53). The NINDS-AIREN recommendations also propose that standardised neuropsychological testing of all neurocognitive domains should be attained (11).

Despite the vast importance of neuroimaging methods which are very sensitive for detecting any type of brain lesions, they cannot differentiate between the patients that will consequently develop cognitive impairment and the ones that will not (16). Lacunar infarcts are detected on magnetic resonance imaging (MRI); they look like areal hyperdensities on T2-weighted sequences, which correspond to hypodensities on T1-weighted and FLAIR sequences (30). Furthermore, microbleeds can be seen on T2-weighted sequences or on susceptibility-weighted imaging (SWI) (47). For brain anatomy evaluation and hypotrophy or atrophy detection the diameter of the brain cortex and hypothalamic area is measured (30). Atrophy can be seen on both MRI and computed tomography scans (30).

Still, our diagnostic skills are far less reliable than ultimate VCI/VaD diagnostic tool – histopathological analysis of the brain post mortem (16).

6.1. Neuropsychological evaluation

In addition to complete medical history, heteroanamnesis and clinical examination, neuropsychological evaluation is a crucial diagnostic tool for determination of cognitive impairment (53). It is equally important for exclusion of other neuropsychiatric diseases (e.g. depression, aphasia) as it is for the assessment of cognitive decline and the determination of its approximate cause (53).

Different cognitive scales are used in clinical evaluation of cognitive function as they permit more accurate neuropsychological evaluation (14,16). The most important features of these scales are good sensitivity for VCI detection and specificity for differentiating VCI from the normal process of ageing and other causes of impaired cognition (55,56) but there are few published validations against a neuropsychological battery. We studied the relationship between MoCA, ACE-R, Mini-Mental State Examination (MMSE.

The Hachinski Ischemic Scale (57) is among the most specific tests for VCI/VaD. This questionnaire consists of 13 statements, the highest score being 18. If a cognitively impaired patient scores 4 points or less, the underlying cause is usually AD, however if he scores more than 7 points, the cause is more likely of vascular origin. Both sensitivity and specificity of the test are about 90 %.

Despite lesser effectiveness in comparison to some other cognitive scales, the Mini Mental Status Examination (MMSE) (55) is one of the most useful tests, and is currently the only validated test in Slovenia. MMSE often underestimates VCI because it comprises only a few tasks for executive functions evalua-

tion. One of the validation studies shows that its sensitivity for VCI is quite low, 70 % at a cross-section value of 29/30 points (56). Therefore, the Clock Drawing Test (CDT) (58) and object tracing are additionally used. Nevertheless, none of these tests is sufficiently specific to distinguish VCI from other dementia aetiologies (15,16).

There are two more accurate cognitive scales for VCI detection, the Montreal Cognitive Assessment Scale (MoCA) (59–61) and the Vascular Dementia Assessment Scale (VaDAS-Cog) (62), however, the latter is not translated to the Slovene language. Both include the tasks for the assessment of memory, executive functions, visuo-spatial processing, abstract reasoning and attention (56,62). Sensitivity and specificity of MoCA are optimal in cross-section value of 25/30 points. At this value, the sensitivity is 77 % and specificity 83 % (56).

Another proven scale for cognitive impairment evaluation is the Frontal Assessment Battery (FAB) (63). Although the median score of FAB does not significantly differentiate AD from VaD patients, there are two subtests of FAB which do. In comparison to AD, VaD patients perform significantly worse in the motor series "Luria" test and the test of conflicting instructions.

7. Primary and secondary prevention

The main goal of primary prevention is to lower the incidence of VaD by early diagnosis and optimal treatment of underlying causes and risk factors (64). It is important to address treatable risk factors such as AH, cardiovascular disease e.g. atrial fibrillation, smoking, dyslipidaemia, DM and elevated homocysteine levels (15,65). Lowering the burden of these will significantly lower the risk of stroke, and consequently of VaD (15,66). On the other hand, the purpose of secondary prevention is to prevent the occurrence of recurrent stroke and to decelerate the development of cognitive impairment (64). Beside appropriate treatment of AH and dyslipidaemia, quick stroke recognition, reperfusion therapy and good rehabilitation are vital components of secondary prevention (64).

Regarding primary prevention, appropriate diet reach in folates and vitamin B12 plays an important protective role against cognitive impairment. Balanced antioxidant intake is also important (67,68). Moreover, studies have shown that high homocysteine levels significantly increase the risk of dementia or cognitive impairment (67,69). Also, the Mediterranean diet has been shown to lower the risk of dementia (70), and the diet reach in fish to even increase cognitive abilities (71).

Apparently, there is an inverse relationship between the level of social interaction in the elderly and cognitive impairment (67). Mental and physical activities have protective effects on dementia and on the development of cognitive impairment (15,65,67). Living an active life, travelling, gardening, crocheting etc. included, can also be beneficial (15,65,67). Therefore, the fundamental feature of stroke and consequently of cognitive decline prevention is the encouragement of the population at risk to live healthy and active lives.

7.1. Harmful effect of arterial hypertension

High systolic blood pressure increases the risk of dementia (72,73). The most important finding of the Syst-Eur Trial is that the treatment of isolated systolic hypertension in the elderly lowers the

incidence of dementia (72); dementia was prevented in 19 of the 1000 cases, who were appropriately treated with antihypertensive therapy for 5 years (72). Another large study on systolic hypertension in Europe has found that AH treated with calcium channel blocker nifedipine reduces the risk of VaD by 55 % (35).

Furthermore, the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) has revealed that the treatment of AH in patients after a stroke with perindopril in combination with indapamide significantly lowers the risk of dementia (64). A similar pattern was seen in a population of patients without previous stoke, where the same treatment decreased the risk of milder forms of cognitive impairment by 19 %, while the risk was decreased by 45 % in a population of patients after a stroke (64). In addition, monotherapy has been found less effective than the combination of therapy in AH treatment (64). However, the median volume of white matter lesions was significantly reduced in patients treated with perindopril alone or in combination with indapamide (74). The research group have concluded that active treatment of AH with perindopril stops or at least decreases the progression of white matter lesions (74).

A systematic review of the effects of AH treatment on dementia has shown that it is generally beneficial for AH and dementia (73). Calcium channel blockers, diuretics, and angiotensin convertase enzyme inhibitors (ACEi) have been mostly studied: diuretics and ACEi have been found significantly more efficient in decreasing the risk of the occurrence and development of dementia than calcium channel blockers (73).

7.2. Harmful effect of dyslipidaemia

Another important drug in secondary stroke and atherosclerosis prevention are statins (HMGCoA reductase (3-hydroxy-3-methylglutaryl-coenzyme A) inhibitors).

In an epidemiological study (75) statins have been shown to significantly reduce the risk of dementia development in the population aged 50 and over. Similarly, Hajjar and co-workers (76) have observed a lower dementia prevalence and decrease in progression of cognitive impairment in patients treated with statins. Results of many studies have confirmed these findings claiming that statins decrease the risk of dementia and cognitive impairment regardless of the type of underlying pathology (64).

Therefore, the question arises as to which mechanism of action enables statins to act as a good preventive therapy against dementia. One study on rats has suggested this could be neurogenesis. The group of rats which was receiving 5 mg/kg simvastatin for 4 weeks had a higher number of pyramidal cells in comparison to the control group. Furthermore, the study group rats performed better on cognitive tests, and were less depressed (77).

8. Symptomatic treatment of vascular dementia

Currently, there is no causal treatment for VCI and VaD. However, there are medications approved for symptomatic treatment of cognitive decline – the same as for AD (44), which are used in combination with preventive therapy of stroke, as well as some experimental drugs (64).

8.1. Cognitive modulators

This group of drugs consist of AChE (acetylcholinesterase) inhibitors e.g. donepezil, rivastigmine, galantamine, and glutamate NMDA (N-methyl-D-aspartate) receptor agonists, e.g. memantine.

Cholinergic deficit in VaD could be explained either by ischemic involvement of basal nucleus of Meynert or by defects in cholinergic transmission caused by vascular lesions (10). Treated with donepezil, patients showed a statistically significant improvement in cognitive function as well as in everyday life (12). Two important clinical trials (78,79)have come to a similar conclusion finding that donepezil easily crosses the blood brain barrier (BBB), is tolerable in terms of side effects, and importantly improves cognition. Methodologically, they administered 5–10 mg of donepezil to the patients for 54 weeks. Additionally, Malouf and Birks (80) have reported cognitive improvement in more than 1200 patients treated with donepezil.

The effect of another AChE inhibitor – galantamine on cognitive function has also been studied (81) . It has been found that it significantly improves behavioural changes and quality of life in comparison to placebo. The therapeutic effect of galantamine has been observed in patients with probable isolated VaD as well as in patients with mixed dementia (81). The Trial GAL-INT-26 (82), included 786 patients treated with galantamine. The results of Alzheimer's Dementia Assessment Scale (ADAS-Cog) were obtained and analysed showing significant cognitive improvements in VaD patients (82).

Moreover, patients treated with rivastigmine showed significant improvements in executive functioning and behavioural changes. The study consisted of caregivers of dement patients. The caregivers taking care of the rivastigmine-treated patients reported lesser stress in comparison to those taking care of aspirin-treated patients (83). Moretti and co-workers (84) have additionally demonstrated improvement in Clock Drawing Test and overall behaviour of patients treated with rivastigmine.

Similarly, patients suffering from mild to moderate VaD and treated with memantine performed significantly better than patients in the placebo group on ADAS-Cog neuropsychological evaluation (83). Another clinical trial concluded that memantine (10 mg/day in two separate doses for 28 weeks) improved cognitive function in patients with mild to moderate VaD (85).

Despite encouraging findings, a meta-analysis by Kavirajan and Schneider (83) has not confirm beneficial effects of cognitive modulators. They analysed wanted and unwanted effects of AChE inhibitors and memantine, and showed little or no benefit on cognitive improvement of VaD patients. Further analyses were suggested, yet there are not sufficient data to support the use of cognitive modulators in clinical practice (83).

The use of cognitive modulators has also been recommended in the Slovenian guidelines for dementia assessment, however they have not been approved for the treatment of VaD or VCI (53).

8.2. Experimental treatment

Most of experimental treatment trials are yet in preclinical phase. Different methods are being studied e.g. endothelial progenitor cell transplantation (86), bone marrow stromal cell transplantation (87), cord blood stem cell transplantation (86). It is presumed that by triggering the release of trophic factors the white matter remodelling would occur enhancing angiogenesis and neurogenesis (12).

Tumour necrosis factor alpha (TNF-alpha) inhibitors are also considered a possible future treatment option. By inhibiting TNF-alpha the inflammatory response can be modulated that might positively affect the hippocampus thus reducing memory problems (12,88,89). Furthermore, resveratrol has been found to reduce oxidative stress in rats; its action is anti-inflammatory and anti-apoptotic, thus it might essentially reduce cognitive decline (87,90).

9. Rehabilitation

Cognitive training and rehabilitation are both the methods of non-pharmacologic therapy. In a systematic review of 11 published articles Fuchs and co-workers have concluded there is still not enough evidence regarding the benefits of cognitive training (91). The lack of evidence could be due to technical issues e.g. different methods of measurement, distinct definitions, and to poor quality of existing evidence (91). The results of a single study of individual cognitive rehabilitation are promising, though preliminary in nature (91). Yet none of the studies has reported side effects. Further studies of cognitive training and cognitive rehabilitation are required to provide more definitive evidence (91).

Finally, it is important to emphasize the speech and language training when discussing cognitive rehabilitation. Some evidence suggests that the logotherapeutic approach can ameliorate functional and neurologic changes after a stroke reducing aphasia to some degree (92).

10. Conclusion

Cognitive impairment is a common feature of stroke regardless of the size or location of the vascular lesion. One in every five patients develops severe cognitive impairment, the so-called vascular dementia, which affects their quality of life.

There is no cure for cognitive impairment. Symptomatic treatment for vascular dementia is similar to the treatment of Alzheimer's disease. Major risk factors for vascular cognitive impairment are modern age diseases which can be easily prevented by living a healthy lifestyle and taking preventive medications.

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