VASCULAR DEMENTIA: THE RELATIONSHIP WITH CARDIOVASCULAR DISEASE, CHARACTERISTICS IN ELDERLY AND PREVENTION. A LITERATURE REVIEW.

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Kaunas, 2018

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SUMMARY

Evalda Tavares, Vascular dementia: The relationship with cardiovascular diseases, characteristics in elderly and prevention. A literature review. The aim of this thesis is to perform a literature review regarding the peculiarities of vascular dementia in elderly and relationship to cardiovascular diseases and its prevention. Objectives:

1. To discuss cardiovascular risk factors for vascular dementia in elderly;
2. To evaluate characteristics of clinical symptoms and diagnosis of vascular dementia;
3. To evaluate management and prevention of vascular dementia in elderly.

A comprehensive literature search was performed to detect articles regarding vascular dementia, the risk factors, its relationship with cardiovascular disease and prevention. Databases used were PUBMED/NCBI, Science Direct and BMJ journal using the search terms: “vascular dementia”, “dementia”, “cognitive decline”, “hypertension”, “heart failure”, “elderly”, “risk factors”, “cardiovascular disease”, “prevention”. There were no quality assessments concerning the included studies.

It is well known that Cardiovascular diseases especially, hypertension, diabetes and heart failure, play a role in development of dementia and many studies confirm this. The overlap between Alzheimer’s and Vascular dementia is great when talking about etiopathogenesis, risk factors and clinical symptoms. Although Vascular dementia may differ in early presentation with milder memory deficit compared to Alzheimer’s disease, it is still difficult to tell them apart since diagnosis is made often late in the progress and both diseases more often coexist than not. Diagnosis criteria for VaD are many and studies have shown that the different methods do not identify the same patients.

Since a cure for Vascular dementia is far from being discovered, acting now on dementia prevention, intervention, and care, with particular attention on modifiable risk factors and management of cardiovascular disorder, is the goal of management. This will vastly improve living conditions for older individuals with dementia and their families. However, further research is still needed to find the most effective methods of dementia prevention.
ACKNOWLEDGMENT

The author wants to express her gratitude towards the supervisor of the work, lecturer Jurgita Knašienė, for the opportunity to learn about this interesting topic also for being so patient.
CONFLICT OF INTEREST

The author reports no conflicts of interest.
ABBREVIATION

AD- Alzheimer’s disease

ADL- Activities of daily life

BP- Blood pressure

BPSD- Behavioral and psychological symptoms

BZD- Benzodiazepines

ChEIs- Cholinesterase inhibitors

CI- Cognitive impairment

CVD- Cardiovascular disease

CVRF- Cardiovascular risk factors

CT- Computed tomography

HF- Heart failure

MetsS- The metabolic syndrome

MRI – Magnetic resonance imaging

SSRI- Selective serotonin reuptake inhibitors

VaD- Vascular dementia

WML- White matter lesion
TERMS

*Aberrant motor behavior*- Movement patterns differing from the usual or norm, abnormal.

*Abulia* – Lack of will or willpower, inability to make decisions.

*Agnosia* - Loss or diminution of the ability to recognize familiar objects or stimuli usually as a result of brain damage.

*Apathy*– Lack of feeling or emotion, impassiveness, indifference lack of interest or concern.

*Aphasia*- Loss or impairment of the power to use or comprehend words usually resulting from brain damage.

*Apraxia* - Loss or impairment of the ability to execute complex coordinated movements without muscular or sensory impairment.

*Cortical lesions* - Lesion in the cortex of the brain.

*Demyelination* - Loss or destruction of myelin, the layer around axons of some neurons.

*Focal signs* - are impairments of nerve, spinal cord, or brain function that affects a specific region of the body such as hemiparesis, lower facial weakness, Babinski sign, sensory deficit, hemianopia, and dysarthria

*Hallucinations* - Perception of objects with no reality, an unfounded or mistaken impression or notion.

*Hemineglect* – Condition following brain damage in which individuals fail to be aware of items to one side of space.

*Hypercapnic* – Abnormally elevated carbon dioxide levels in the blood.

*Leukaraiosis* - Ischemic demyelination or age-related white matter disease.
Macrovascular changes- Disease of any large blood vessels in the body, including coronary arteries, the aorta, big arteries of the bran and in the limbs.

Microvascular changes- Changes in the part of the circulatory system made up of small vessels such as venules or capillaries.

Mood disorder- Mood disorders are mental disorders characterized by periods of depression, sometimes alternating with periods of elevated mood.

Pseudobulbar palsy – Involuntary emotional expression disorder, inability to control the muscles of face.

Subcortical lesions- Lesions involving or being a part of the brain below the cerebral cortex.

Visuospatial difficulty- Difficulty to process thought that involve visual or special (involved in the perception of relationships of objects in space).
INTRODUCTION

Development in medicine and healthcare in recent years is partly responsible for the increase in life expectancy in the worldwide population, and with that follows an increase in the disease associated with aging, and among that dementia. [8] Vascular dementia (VaD) is the second most common dementia form after Alzheimer’s disease (AD), accounting for up to 20% of all dementias. [1]

Cardiovascular disease (CVD) such as hypertension, diabetes, hyperlipidemia, heart failure (HF), play an important role in the etiology of dementia. Stroke is one of the risk factor for VaD with studies revealing that 1 in 10 patients develop dementia shortly after a stroke. Although CVD may lead to stroke, CVD seem to be an independent risk factors in developing dementia [16].

Up to this point attempts of changing onset or progression of dementia has been unsuccessful, although many trials including anti-AD drugs have been conducted, all results have shown that the drugs are not as efficient for VaD as for AD. Therefore, none have been approved for use in VaD, leaving the focus on intervention of cardiovascular risk factors (CVRF) in middle age to older age population for dementia prevention [1,35,36].

Dementia has a physical, psychological, social, and economical impact, not only on those who suffer from it, but also on their carers, families and society. [33,45] Due to the accelerating global growth, dementias are set to be one of the biggest public health challenges. The question is no longer if CVD contributes to dementia, there is an expanding body of literature linking heart disease as a risk factor for dementia, particularly if they manifest in midlife, are associated with the development of dementia later in life. Increasing awareness of this problem and incorporating prevention of the risks is crucial [18,28] The purpose of this review is to present the current knowledge base regarding CVD and its relation to dementia in elderly.
AIM AND OBJECTIVES

Dementia is one of the most burdensome medical conditions, not only for the patient and the family but also for healthcare and society. With the aging population growing rapidly, the number of people effected with dementia is expected to double. Dementia research is underfunded in proportion to its impact as a global health crisis. Vascular dementia is the second most common dementia, up to 20% of all dementias. At present, there is no cure for Vascular dementia, making the need for treatment that can either delay or slow the progress of the disease crucial. Hopefully this small contribution will raise awareness in this topic and the relevance to research more on this. The aim of this thesis is to perform a literature review regarding the peculiarities of vascular dementia in elderly and relationship to cardiovascular disease and its prevention.

Objectives:

1. To discuss cardiovascular risk factors for vascular dementia in elderly;

2. To evaluate characteristics of clinical symptoms and diagnosis of vascular dementia;

3. To evaluate management and prevention of vascular dementia in elderly.
Dementia is the most common form of degenerative disease among the elderly, in later stages resulting in total dependence and inactivity, which has ensured a great health burden with high socioeconomic costs. [1]. Vascular dementia (VaD) is the second most common type of dementia following Alzheimer’s disease (AD) accounting for 17-20% of all dementias in elderly. VaD is caused by reduced blood supply to the brain and may or may not be associated with a stroke. [2] The overlap that exist between VaD and AD increases the perplexity not only of diagnosis but also treatment. [3]

No current available imaging technique neither clinical data can accurately distinguish between changes caused by either pathology. It could be said that vascular dementia should not be regarded as a disease which is present isolated, but rather coexistent with multiple pathologies and clinical expressions [4]. The biggest risk factor that contribute to VaD are cardiovascular risk factors (CVRF) and cerebrovascular risk factors [7]. Several studies report that patients with CVRF have higher risk of developing dementia compared to general population. Vascular brain damage due to increased CVRF can be divided into; clinical stroke (damage of large arteries) or subclinical or “silent” brain infarction (damage of small arteries). [8]

VaD can be divided into three main types depending on location of lesion: strategic infarct dementia, multi-infarct dementia, and subcortical vascular encephalopathy. Strategic infarct dementia is caused by one single infarct in an area of the brain resulting in significant cognitive dysfunction. However multi-infarct dementia as the name suggests is characterized by multiple lacunar infarcts and small
and/or large infarcts in the cortex and subcortical regions also resulting in a significant deficit in functional brain capacity [10].

RISK FACTORS

Even if increased life expectancy may be suggestive of a healthier population, the consequences are a higher rate of disease associated with aging, and among that dementia. [4]. Demographic risk factors include age, sex, and education. Although dementias are not a part of normal aging, age is the greatest known risk factor. The frequency of VaD is known to increase with age, 65 and older. When interpreting this data have in consideration that there is not a consensual diagnosis criteria and diagnosis differ in-between regions of same country, making prevalence less reliable. And when coming to gender the predominant conclusion is that men are at higher risk than women in all age groups, on the contrary to AD where woman have higher incidence especially after 90 years. [5]

In clinical studies the prevalence of VaD ranges from 4.5 to 39%, both incidence and prevalence increase with age and may slightly decrease after age 95. Studies all around the world show big differences, considering the difficulties in diagnosing VaD, and studies must therefore be interpreted cautiously [6].Education is reported to be protective, but whether or not this is a result of the association of higher education, with higher income or occupation type, remains to be determined. A great number of studies have been done during the years all showing different results. The education-dementia relationship was more supported in developed countries compared to developing areas. This finding may be intriguing as developing regions have an older population who are uneducated or poorly educated, yet the prevalence of dementia is much lower. [11] The impact of education during late life and importance of intervention programs on the effect on dementia remain unexplored. [62]
Atherosclerosis risk factors include hypertension, cigarette smoking, myocardial infarction, diabetes mellitus and hypercholesterolemia [12]. Atherosclerosis is the aging processes of the vessels resulting in deposit of cholesterol plaques on the intima of the large to medium vessels. These plaques calcify and occlude the lumen, disturbing blood flow and making the vessel susceptible to rupture. Which may later result in thrombosis and even thromboembolism, leading to myocardial infarcts and strokes. [7]

A postmortem grading of circle of Willis atherosclerosis was performed including 397 subjects, 92 controls were non-demented, 215 had AD, 30 with VaD and 60 with other dementias. The VaD subjects were older with a mean age of 86.7 years. Severity of atherosclerosis was higher among AD and VaD subjects, and equal between control subjects and subjects with non-AD dementias. VaD group had significantly greater atherosclerosis The results suggest that high atherosclerotic grade increased the risk for the diagnoses of VaD. Lifestyle modification and pharmacology therapy are proven to address complications of atherosclerosis, could be reasonable that the same therapies may delay progression of VaD. [12]

Other risk factors associated with dementia include cerebral infarcts, white matter lesions as well as atrophy of brain. White matter makes up about half the brain and is involved in over 100 disorders, of which all produce neurobehavioral sequelae due to dysfunction of white matter, most likely resulting in dementia [13]. White matter areas are especially sensitive to circulatory dysfunction and hypercapnic states the brain further reduces cerebral oxygen from white matter. And this potentially extends the white matter changes. [14]

The number of deaths from stroke this past decade has declined while surviving rates are growing. Making them at increased risk of cognitive dysfunction. Studies show that 1 in 10 patients developed dementia shortly after a stroke and 1 in 3 being demented after a repeated stroke. Despite the fact that not all strokes necessarily lead to dementia, it is still a common risk factor and is not to be confused with the state of delirium presently following stroke as consequence of the injury. Compared to other
neurological deficits as motor or sensory dysfunction, dementia or cognitive impairment is till neglected after stroke. [9]

VaD is a complex disease and genes influencing risk of “pure” vascular disorders have been difficult to identify. But the disease may follow after stroke and has many similarities with AD some genes affiliated with these two diseases may also result in distinct forms of VaD. The familial stroke gene retinal vasculopathy with cerebral leukodystrophy (RVCL) which presents with visual loss, stroke and dementia in middle age in people affected, is one of the genes thought to be linked with VaD. Familial AD genes such as Amyloid precursor protein gene (APP) and presenilin 1 (PSEN1) and 2 (PSEN2) genes are believed to affect the development of VaD, but more research is needed. The most common genetic risk factor for both AD and VaD is the apolipoprotein E (APOE). APOE plays a role in lipid transportation including cholesterol redistribution, oxidative stress, tau phosphorylation and beta-amyloid clearance and aggregation. There are 3 types of APOE- ε2, ε3 and ε4, the ε4 allele of APOE has been the only one associated with VaD. Meta-analysis showed 3-fold increased risk to develop AD if carrying one copy of ε4 allele and 15-fold risk in homozygote individuals. [5]

Most common genetic mutation affiliated with vascular dementia and other types of dementia is the CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy) which is caused by a mutation in NOTCH-3 family gene which creates residue of a receptor protein in cerebral arteries. The accumulation of this protein result in cerebral infarctions. [5, 15] There are other hereditary traits, but they are even more rare.

CARDIOVASCULAR DISEASE RISK FACTORS

CVDRF such as hypertension, diabetes, hyperlipidemia, heart failure (HF), play a pivotal role in the etiology of dementia in elderly. Although stroke causes dementia, CVDRF appear to be independent risk factors in developing dementia. [16]
Hypertension

Vascular factors participate in all major causes of cognitive impairment (CI) in older people, and VaD being the most extreme case of CI. Hypertension effects the regulation of the cerebral circulation by reducing blood flow to the brain leading to ischemic injury which in turn impair brain structure and function. Experimental finding showed that by inhibiting renin, the enzyme that converts angiotensinogen to angiotensin 1, the brain was protected from WML which is associated with CI. [17] A pathological study evaluated autopsy of 1110 demented elderly subjects, in total 44,1% had AD, 25,7% AD + cerebrovascular lesions, 10,8% had VaD and the rest was mixed pathologies. Among the VaD autopsy 92% showed signs of hypertension, 61,3% showed morphologic lesions associated with diabetes, 52% showed history of myocardial infarction and 58,4% showed cardiac decompensation. [10]

A study where they followed up 232 older subjects for a period of 17 years with blood pressure (BP) measurements. 123 developed AD and 76 developed VaD. They evaluated the link between late and mid-life BP levels and the risk of dementia later in life. Results shows that the risk of VaD increase greatly with elevated systolic BP levels in both late life and midlife. Every 10-mm Hg raise in systolic BP in late life and midlife was correlated with an 18% and a 24% higher risk of VaD occurring, respectively. The same tendencies were observed with diastolic BP levels in mid-life but not for late life. [18]

In one survey from 2008 comparing association of high blood pressure, hypertension with poor cognitive function in persons 60 and older showed that individuals with hypertension had the poorest performance in all age groups except the oldest group 80 and older. The high blood pressure group of subjects aged 60 to 64, and 65 to 69, was associated with poorer cognitive performance. The group
with optimal blood pressure (<120/80 mmHg) had the best performance. In those aged 75 to 79, best performance was in subjects who were pre-hypertensive and in the ones aged 80 and older best performance was for the group with moderate hypertension. [32] Hypertension is sure associated with cognitive decline but this study tells us that its not so in all age groups, in older subjects a higher blood pressure may be for the better, and this should be taken into account when regulating blood pressure in older subjects.

Diabetes

Diabetes have frequently been proven to increase the risk for cognitive failure and dementia. The mechanism behind this is not entirely understood. Micro- and macrovascular changes are common complications of diabetes leading to changes in many organs and among them the brain. Microvascular changes are associated with cortical atrophy and macrovascular changes affect brain function by occlusion and ischemia, both leading to CI. [19,20]

A 10-year population-based study among older Mexican-Americans found that diabetes is associated with a twofold increased risk of dementia, in both untreated and treated diabetes. Other studies conducted in white elderly populations, like the finish study in the city of Vantaa including subjects aged 85 or older showed same result. Data reports that diabetes doubles the risk of dementia by the fact that these subjects were more likely to develop vascular pathology and have cerebral infarcts. Further confirming the allegations that elderly patients with diabetes are at an increased risk of VaD. [21,22]

Heart failure
Although dementia and HF can coexist, the relation between these two diseases is uncertain. A Swedish population-based study found a 1.8-fold higher risk of dementia in HF individuals aged 75 years and older compared with individuals without HF. Another study revealed that late-life HF was associated with a doubled risk of dementia. Causing mechanisms are still unknown. Low cardiac output, neurohormonal activation and alterations in autonomic control might result in chronic cerebral hypoxia which in turn may contribute to the pathogenesis of dementia. [23,24,25]

A Danish population-based study over 35-year follow-up in patients with late life HF (the mean age of 77), found that the risk for VaD and other dementias was higher in the male group with HF patients under age 70 than in members of general population. The risk seemed somewhat less strong for dementia in patients under 70 than in patients above 70. Also risk was increased for both men and woman but slightly higher in men. [23]

However, a Finnish study of HF patients showed no association between midlife HF and late onset dementia, and had similar results as other studies when comparing patients with late-life HF. It is well known that HF has various vascular risk factors and that may explain the observed increased risk of VaD in elderly. Also HF studies indicate that patients are at a great risk to suffer from a stroke, atrial fibrillation, diabetes and hypertension all of which are greatly linked to dementia. [26,27,28]

Metabolic syndrome

The metabolic syndrome (MetsS), is a collection of CVRF that include abdominal obesity, hypertension, insulin resistance, and dyslipidemia, and has been shown to be associated with both clinical and silent strokes by two- to fourfold. MetS is associated with high levels of inflammation which contributes to faster atherosclerosis and in turn either the atherosclerosis or inflammation or
both contribute to CI. Although the exact mechanism is unknown, speculations are that MetS contributes to VaD by causing microvascular damage with following WML and disrupted cortical structure. [63]

In older studies data showed a weak relationship with VaD, newer cohort study found a stronger association. In the Italian Longitudinal study on ageing working group, participants aged 65-84 were studied with a 3,5year follow-up. MetS subjects compared to non-MetS subjects had an increased risk for VaD. The risk increased by another 50% when those with high inflammation and MetS when compared to those without MetS and inflammation. [63]

Another study investigated the association of MetS and occurrence of dementia in older adults before and after age of 75, data showed that the overall risk of dementia was not associated with MetS in those younger than 75. In the older subjects MetS was associated with a lower risk of AD but not VaD, and abdominal obesity was rather associated with a lower risk of overall dementia. MetS is not associated with dementia after 75, on the contrary MetS may even be associated with a lower risk for dementia. [79] So far the association of MetS with dementia have been weak and more research in this field should be conducted. Investigation on the lowered risk should be further discussed.

CLINICAL SYMPTOMS

Clinical manifestations of VaD are many, depending on the affected part of the brain by the vascular pathology. Two clinical patterns are known, cortical and subcortical. Cortical syndrome may be present with clinical stroke and depending on area can present as such:

- Medial frontal infarct manifestations are abulia, executive dysfunction, abulia or apathy.
- Left parietal can manifest as apraxia, aphasia or agnosia.
- Right parietal often manifest as hemineglect, visuospatial difficulty, confusion and agitation.
- Medial temporal infarcts manifest as anterograde amnesia. Patient may improve before the next episode; the course is therefore recognized as stepwise.

In subcortical pathology the deep cerebral nuclei and WM are affected by lacunar infarctions or chronic ischemia. Features of the subcortical syndrome include: memory and attention deficit, abnormal executive function, pseudobulbar palsy, gait disturbance and psychomotor retardation. Personality and mood changes such as depression, apathy and emotional incontinence are common. History of unprovoked and recurrent falls, also urinary problems not explained by urologic disease is frequent. The course may be slow or fast in decline. [29]

Behavioral and psychological symptoms of dementia (BPSD) are common in elderly, including mood disorder, agitation, irritability, wandering and sleep problems. Some studies show that older patients with a younger mean age have higher prevalence of BPSD symptoms (<75year 24-40% and in 75+ years 9-22%). Symptoms correlate with the severity of dementia and seem to be more prevalent in moderate and severe VaD, studies estimate that 50-80% of older subjects with VaD suffer from these symptoms at some point during their illness. These symptoms have a negative effect on quality of life of both patient and their caregivers. [30]

A large clinical trial investigating the prevalence BPSD in VaD subjects with a mean age of 72, reported that 92% of patients had such symptoms. Apathy was the most frequent and was present in 65%, depression, irritability and aggression/agitation followed with over 40% prevalence. Results also demonstrate that small-vessel VaD has a different profile of BPSD compared with large-vessel VaD. Apathy, aberrant motor behavior and hallucinations were more severe and more common in small-vessel VaD while agitation/aggression were more severe in large-vessel VaD. [31]
DIAGNOSIS

For the diagnosis of VaD a systematic approach is recommended, including history taking not only from the patient but also from close family members/ friends, cognitive testing, blood tests to exclude other comorbid systemic illness that can be reversible, such as hypothyroidism or folate and B12 deficiency anemia. Also infections such as Syphilis and HIV are mainly excluded. In the history taking questions should focus on memory loss, although forgetting is normal and even more normal in aging people. Important to question closer relatives because if the patient is having memory problems he/she may not remember or even be to ashamed to admit it. [33] Those with dementia will forget thing such as appointments, or family occasions more often and will not even remember them later. Disorientation to time and place like getting lost in their own street, or not knowing how they got to one place and later not knowing the way back home is common. Isolating themselves, sleeping more than usual or being more dependent on family member is another sign that most often can be present. Rapid mood swing and acting suspicious and fearful are other signs that may be present but wont come up unless you ask for it. History talking could include following questions: “Would you leave him/her alone for 2 weeks, would him/her manage alone – why/why not?” “would he/she manage to cook a meal for the family?” If answer is no family member is stating that the patient depends on family for everyday living and is unable to take care of her/himself.

Screening the cognitive function is most often done by the Mini-Mental State Examination (MMSE). Its not only used for screening but also for tracking any change over time in cognitive function and assessing the effects of any administered drug. MMSE has been a subject of many studies and publications and is deemed to be a sensitive marker of dementia. The MMSE is a paper-based test with a maximum score of 30, the lower the score the more severe cognitive problems the patient will have. The cut point for normal scoring is usually 24. Results of the MMSE should be interpreted and adjusted in presence of level of education and literacy skills, language, and any current motor, hearing, and visual impairment. [33] In a study where they did the MMSE test in highly educated patients to detect cognitive dysfunction results showed that the cut point of 24 is not optimal and instead a score of 27 yields greater accuracy for identification of early dementia. The data is not enough because the
sample was small and homogenous, there is a need of further examination especially across ethnic groups, also the study MMSE was not done for dementia diagnosis and may differ when done in dementia investigation settings. [80]

Neuroimaging should be done to diagnose VaD especially in patients with stroke history, CVRF and abnormal neurologic examination. And also because the criteria’s for VaD discussed bellow require evidence of cerebrovascular disease. MRI is more sensitive than CT, on showing signs of VaD such as subcortical and cortical infarctions, ischemic changes or leukoaraiosis. WML is not specific for VaD and is also associated to nonvascular pathology including demyelination, neoplasia, infection. MRI has a 80% sensitivity and specificity for differentiation of different types of dementia such as AD from VaD or dementia with Lewy bodies. [33] It was previously assumed that the total volume of infarcts was the main indicator for VaD, but its clear now that multiple microinfarcts as well as small ischemic lesions correlate better with VaD risk. And location is of more importance than volume of lesions. Infarcts that have greater involvement of the dominant hemisphere alters the risk of dementia. [34]

There are many different diagnostic criteria proposed in the diagnosis of VaD. The Hachinski ischemic scale (HIS) seeks to predict the dominant underlying pathology and is based entirely on the history of CVRF and on clinical signs, table 3. It was widely used in earlier studies, and patients are more likely to have VaD with score of 7 or more, and with a score of less than 4 VaD can be excluded. Is is considered a sensitive specific marker for the diagnosis of VaD although the criteria does not have imaging criteria, but in combination with imaging could be reliable in indication of pathophysiology. [8]

The National Institute for Neurological Disorders and Stroke-Association Internationale pour la Recherche et l’Enseignement en Neurosciences (NINDS-AIREN), table 2, is the vastly used in research settings. The main features for this criteria is (1) acute onset of dementia, demonstrated by impaired of memory and two other cognitive domains (2) Significant evidence of cerebrovascular
lesion on neuroimaging and (3) temporal relation between stroke and cognitive loss. The International Classification of Diseases (ICD-10) criteria for VaD further differentiates it into subtypes (VaD of acute onset, multi infarct dementia, Sub cortical VaD and mixed or unspecified types) making the ICD-10 criteria rather selective and lacks detailed guidelines for clinical signs and brain imaging requirements. Both NINDS-AIREN and ICD-10 have a high sensitivity for probable VaD. Others are the diagnostic and Statistical Manual of Mental Disorders (DSM-5), table 2. Cardinal factors between the criteria were requirement of (1) focal neurological signs, (2) unequal distribution of deficits in higher cortical functions, and (3) evidence of relevant CVD on brain imaging findings. Nonetheless, a number of studies have shown that the different criteria do not identify the same patients. [34].

Table 1 The Hachinski Ischemic score

A high score (≥7) suggests vascular dementia, while a low score (≤4) suggests Alzheimer disease. Adapted from cerebral blood flow in dementia hachinski et al september 1975.

<table>
<thead>
<tr>
<th>FEATURES</th>
<th>VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABRUPT ONSET</td>
<td>2</td>
</tr>
<tr>
<td>SETPWISE DETERIORATION</td>
<td>1</td>
</tr>
<tr>
<td>FLUCTUATION</td>
<td>2</td>
</tr>
<tr>
<td>NOCTURNAL CONFUSION</td>
<td>1</td>
</tr>
<tr>
<td>RELATIVE PRESERVATION OF PERSONALITY</td>
<td>1</td>
</tr>
<tr>
<td>DEPRESSION</td>
<td>1</td>
</tr>
<tr>
<td>SOMATIC COMPLAINTS</td>
<td>1</td>
</tr>
<tr>
<td>EMOTIONAL LABILITY</td>
<td>1</td>
</tr>
<tr>
<td>HYPERTENSION</td>
<td>1</td>
</tr>
<tr>
<td>HISTORY OF STROKE</td>
<td>2</td>
</tr>
<tr>
<td>ASSOCIATED ATHEROSCLEROSIS</td>
<td>1</td>
</tr>
<tr>
<td>FOCAL NEUROLOGIC SYMPTOMS</td>
<td>2</td>
</tr>
<tr>
<td>FOCAL NEUROLOGIC SIGNS</td>
<td>2</td>
</tr>
</tbody>
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THE CRITERIA FOR THE CLINICAL DIAGNOSIS OF PROBABLE VASCULAR DEMENTIA INCLUDE ALL OF THE FOLLOWING

- **DEMENTIA**
  Defined as cognitive decline manifested by memory impairment and of two or more cognitive domains (orientation, attention, language, visuospatial functions, executive functions, motor control, and praxis), established by clinical examination and documented by neuropsychological testing; deficits should interfere with activities of daily living not only attributed to physical stroke sequelae.

  Exclusion criteria: Other brain disorders eg. AD that could account for cognitive decline and memory problems. Also cases with consciousness disturbances, delirium, psychosis, severe aphasia, or major sensorimotor impairment impeding neuropsychological testing.

- **CEREBROVASCULAR DISEASE**
  Defined by the presence of focal signs on neurologic examination with stroke (with or without history of stroke), and evidence of relevant cardiovascular disease by brain imaging (CT or MRI) e.g. multiple large vessel infarcts, single infarcts, white or periventricular white matter lesions, or extensive periventricular white matter lesions, or combinations of these.

- **A RELATIONSHIP BETWEEN THE ABOVE TWO DISORDERS**
  MANIFESTED OR INFERRED BY THE PRESENCE OF ONE OR MORE OF THE FOLLOWING:
  a) Onset of dementia within three months following a recognized stroke;
  b) Abrupt deterioration in cognitive functions; or fluctuating, stepwise progression of cognitive deficits.

Adapted from cerebral blood flow in dementia Hachinski et al September 1975.

**Table 2. NINDS-AIREN criteria for probable vascular dementia.**

**Table 3. DSM-V criteria for major Vascular neurocognitive disorder**
<table>
<thead>
<tr>
<th>Vascular dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Cognitive decline in one or more of cognitive domains: learning and memory, language, executive function, complex attention, perceptual-motor, social cognition.</td>
</tr>
<tr>
<td>B. The cognitive deficits interfere with independence in activities of daily living.</td>
</tr>
<tr>
<td>C. The cognitive deficits do not occur exclusively in the context of a delirium.</td>
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<tr>
<td>D. The cognitive deficits are not better explained by another mental disorder (e.g., major depressive disorder, schizophrenia).</td>
</tr>
<tr>
<td>E. The clinical features are consistent with a vascular etiology, as suggested by either of the following:</td>
</tr>
<tr>
<td>a) Onset of the cognitive deficits is temporally related to one or more cerebrovascular events.</td>
</tr>
<tr>
<td>b) Evidence for decline is prominent in complex attention (including processing speed) and frontal-executive function.</td>
</tr>
<tr>
<td>F. The presence of cerebrovascular disease is evident from history, physical examination, and/or neuroimaging considered sufficient to account for the neurocognitive deficits.</td>
</tr>
<tr>
<td>G. The deficits are not better explained by another brain or systemic disorder.</td>
</tr>
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Family physician's role in diagnosis
In reality many people with dementia are never diagnosed, in UK its estimates that 50% of dementia remains undiagnosed. Also many people receive the diagnosis until it’s too late to benefit from interventions. Having a diagnostic confirmation often relieves anxiety compared to not knowing the reason behind the changes which affects the daily life. In UK a strategy was instituted after variations in diagnosis across regions of England were brought into light. First step was a public campaign, including television and newspaper adverts to oppose the belief that a diagnosis of dementia was not beneficial, based on the false assumption that dementia is a normal part aging and that no treatment or support is available. And Second to provide practitioners with the confidence and tools needed to make a diagnosis and lastly target and monitor diagnosis rates at the primary care level. And studies since then have shown an increase from less than 40% before the strategy to 67% 2015. [33]

According to general practitioners (GP) prevalence of CI in patients 70 and older was 4.6% but according to MMSE score the total prevalence was 21%. An analysis done among German primary care patients done on the probably of receiving dementia diagnosis showed that patients may benefit from screening. This is one of the first studies to demonstrate positive effect of screening. This data is not totally reliable since the GPs were all aware of this trial and may influenced their attitude and behavior when participating in the study. False-positive diagnosis I the study was believed to be about 24%. The goal of a positive screening is for an additional assessment of the patient, and to differentiate between several reversible causes. If this is not the consequence of the screening than tables will turn and false-positive diagnosis of dementia will lead to over diagnosis of dementia. The effect of a false-positive diagnosis must be weighted against the harm of not diagnosing dementia. [81]

Performing a population-wide screening program for all of the ageing population is not recommended, primarily due to the uncertain benefits such a program would offer. However, a program regarding case finding for older patients that has been admitted to the hospital to help improve the management and outcomes of dementia should be implemented. This because of the common trend of older people with repeated admissions to the hospital due to a bad general state of health before an actual diagnosis concerning dementia is made. The estimation of patients with undiagnosed dementia in hospitals is
about 40% meaning that patients are being discharged with dementia lacking the proper understanding and compliance of the management plan after the discharge. This is a problem as the key feature of good dementia care is to establish a diagnosis at a time when patients and their carers will benefit from support and interventions. [33, 61]

In the assessment of the diagnosis, it’s important to consider how? and who? made the diagnosis. It is important that the clinician that assessed the patient had experience in dementia. Causes of secondary dementia and other conditions that can mimic dementia must be excluded. Depression in elderly is a good example of conditions which leads to poor global performance and is also known as pseudo-dementia. Also the diagnosis of dementia is sometimes made in old patients who have delirium or CI because of an acute problem, such as an infection. [33]

MANAGEMENT

There is no cure for dementia and psycho-social (non-medicamental) interventions are most appropriate both to provide quality of life and better BPSD of dementia. [35] The focus should be in reduction of risk factors which is the most effective way to potentially delay onset and reduce the number of cases. [36] To this point no drug has been approved for the treatment of VaD. Many anti-AD drugs that improve cognition have been tested, with mixed results.

Cognition

The best studied treatments are cholinesterase inhibitors (ChEIs) which reduce synaptic breakdown of the neurotransmitter acetylcholine, enhancing cholinergic transmission. Research suggests that cerebrovascular injury also damages the cholinergic pathways. Three ChEIs, donepezil, galantamine
and rivastigmine were tested in patients with vascular dementia. All the trials reported positive improvement on cognition but lower effect compared to AD treatment. When looking at activity of daily living (ADL) and neuropsychiatric symptoms no significant effect was noticed. [33, 37] Memantine is an antagonist to glutamate (NMDA) receptors and prevents excitatory neurotoxicity in dementia and is used in AD treatment. It has been tested in patients with VaD and suggest small beneficial effect on cognition, better ADAS-Cog scores, and behavior but as with the other drug trials data are insufficient to support widespread use of these drugs in VaD [38].

Cognitive stimulation therapy (CST) consists of group sessions that integrate simple cognitive exercises, social activity and reminiscence. Studies found that CST benefits on general cognition and have equivalent effect of that in ChEIs, although trials of CST do not involve a placebo group. Its is also cost effective for people with mild-to-moderate dementia, but there are to few follow-up studies to clarify how long effects last. Although it seems to be efficacious, the clinically significant evidence is debatable. [33] Cognitive training consists of training specific cognitive domains, with adaptive levels of difficulty. Relatively few trials exist on this topic. A meta analysis found only four trials that reported positive outcome. [70] Also a Cochrane review found cognitive training to be of no significant value to patients with AD and VaD, suggesting that it may only have benefits in healthy older adults without dementia. [68] However a randomized controlled trial with AD patients, where 18 sessions of 30 minutes training were conducted over 8 weeks resulted in improvement in memory and general cognitive function. [71] Cognitive rehabilitation helps patients improve everyday function by setting individual goals to achieve these. It can be effective for patients with mild dementia where setting specific goals may help with function level. [69]

Nicergoline a potent selective alpha-1A adrenergic receptor antagonist is considered to be useful in cerebrovascular disorders due to it improving cerebral. Currently its been used treatment of vascular dementia and is showed to improve cognitive function and memory and to reduce severity of the disease. The safety evaluation show that these agents are well tolerated and should be further evaluated in trials, as no controlled studies have been done yet on this subject. [82]
Folic acid is known to decrease homocysteine and other inflammatory cytokines levels which are associated with cognitive decline and dementia, several trials on folic acids effect on and dementia have been done but results are still inconclusive. The most recent trial where folic acid supplementation (400μg) was given to patients with mild CI for 12 moths showed significant cognitive improvement. Another trial showed similar results, also improved performance after 36 months of daily oral administration of 800μg folic acid supplements. The optimal dose of folic acid needed to reduce inflammation and improve CI is still unknown, longer interventions with folic acid supplementation might lead to greater changes and should be further researched. [83]

Recent studies have shown a possible role of Citecoline a precursor of phospholipid synthesis in CI, especially of vascular origin, mechanism are not well known but it acts as a neuroprotector. In trials doses of 500mg-2g/day have been administered orally, intramuscular and intravenously and no serious side effects have been reported. Other studies have shown poor result of Citicoline administration but this could be due to short time of administration. All studies done were conducted under short period of time, evidence for the use is strong future studies should target a longer period of use. [84]

Neuropsychiatric symptoms

Agitation

Antipsychotics are used to treat BPSD such as agitation, although they show efficacy in treating these symptoms, their use is limited by their adverse effect profile. Antipsychotic drugs may cause somnolence, urinary tract infection, falls and gait abnormality, extrapyramidal symptoms and an elevated risk of any type of cerebrovascular incidence which is a risk of dementia in itself. Evidence also indicates that antipsychotics are used for periods longer than six months with limited monitoring of adverse effects. [39] A study showed that mortality risk was the highest with haloperidol, data also suggested a dose-response relationship between antipsychotics and risk of mortality. Lastly, findings suggest that the risk of mortality is higher than previously estimates. [40]
Caring for agitated demented people is more difficult and time consuming than caring for non agitated. One should always ask the person what is wrong, but many times demented persons can not say. Causes of agitation include the person being hungry, thirsty, being in pain, delirious, feeling frightened, hot or cold. Overstimulation or unknown environment might also worsen agitation. The best way of decreasing agitation is through communication and other social interventions. Trials shows that with social interventions the agitation is decreased not only short term but up to 6 months afterwards. [74] Agitation may be a result of boredom, so engaging in meaningful activities improve overall brain health through building neural connections, and also gives the elderly a sense of purpose and meaning. Also studies reveal that social activities such as music therapy, or sensory interventions including massage in care homes decrease agitation, there was no evidence that the effect lasted beyond the intervention. [72] Also live social stimuli such as visit from a baby or a pet increased pleasure opposed to dolls or robotic animals. Also unpleasant stimuli experienced as an invasion of personal space or threat might cause agitation, as when helping person with personnel hygiene. [33]

Depression

Antidepressants are often used to treat depression in older dementia patients and despite the frequent use of these, very little evidence for their effectiveness is available. Trials have shown that if there is a positive role, it is weak. Also there are no good evidence improving other outcomes, such as ADL, cognition or clinical severity. [41,42] Trials show that selective serotonin reuptake inhibitors (SSRI) are associated with the highest risk of falls in older population compared with when antidepressants were not being used. Other groups of antidepressants such as tricyclic antidepressant and monoamine oxidase inhibitors were associated with the highest risk of mortality, attempted suicide/self harm, stroke/transient ischemic attack, fractures, and epilepsy/seizures, compared with when antidepressants were not being used [43].
Psychological therapy is suggested in depression, but evidence for its effectiveness in demented patients is inconclusive. A meta-analysis involving demented participants with depression or depressive symptoms found out that therapy showed effectiveness in reducing depressive symptoms, but the quality of evidence was low. [76] Engaging in meaningful activities might reduce depression. The reducing disabilities in AD program included exercise training, education of carers and problem solving. Results found that this combination improved the physical disability and also improved the depressive symptoms, although clinically insignificant. However, the combination makes it hard to decide if exercise is the active component. More research is needed. [73,75]

Sleep disturbances

Dementia patients in care facilities take benzodiazepines (BZD) or other non benzodiazepine sedatives e.g. Zopiclone to help with sleep disturbances. Data suggest that patients taking hypnotics had worse sleep quality and did not have better outcomes than those not taking hypnotics. BZD also increase the risk of falls and mortality in the older population. Thus, without definite benefits, and with strong evidence of harm, benzodiazepines should be avoided, if possible. [44].

A trial with 36 participants suggest that light therapy, activity and behavioral techniques could help sleep. Evidence about light therapy and sleep hygiene are insufficient, studies are rather small. As there is no one treatment that have evidence of effectiveness, using a mix of hygiene measure, medication and activity is best. [33,77]

Care for people with dementia

In most cases families care for elders with dementia living at home. This care is not only physically demanding but very psychologically demanding, a Japanese study show that caregivers suffer more frequent from depression, insomnia, anxiety and pain compared to non-caregivers. [35,45] These
psychological symptoms in caregivers is what can lead to institutionalization. [46] Meta-analysis show effectiveness in delaying institutionalization of the older patients by involving caregivers in making choices about treatment and developing different support programs. [47]

In care facilities person-centered strategies are the essential in the care for persons with dementia, care that is individualized, empathetic and provides a supportable social environment. The focus should be on supporting independence of the elderly population, continue engagement in meaningful activities and educating not only the person and their careers but also care workers. Planning for future care based on the individual’s wishes is important, therefore the importance of early diagnosis. As the condition progresses, aggressive and invasive treatments should be balanced against the impact on the quality of life for the person with dementia [48]. Two trials have shown that educating staff in person-centered approaches care for people with dementia led to significant improvements in quality of life and reductions in psychological symptoms of dementia and agitation [48,49].

PREVENTION

Performing a population-wide screening program for all of the ageing population is not recommended, due to the uncertain benefits such a program would offer. As there is no cure, modification of risk factors is the most important in prevention. [33] Studies that use one single RF intervention in the prevention of dementia show mixed results, with some positive results but many studies proved ineffective. Therefore, studies which target multiple RF and treatments in combination are more likely to be effective than one single RF intervention. [1] The most ideal prevention-treatment approach to reduce VaD prevalence or severity, is considering the wide-ranging clinical features and not just the presenting symptoms as depression, agitation, cognitive decline.
Prevention should be divided into: primary, secondary and tertiary prevention. [8] Primary VaD prevention should include modifying daily life styles such as: smoking, diet, and physical exercise. One Multi-ethnic cohort study revealed that heavy smoking in middle-age doubles the risk of later-life dementia. Also quitting smoking may reduce the risk of dementia to levels of non-smokers [51] When it comes to diet, data from observational studies show a protective role for certain nutrients, such as omega-3 fatty acids, antioxidants or B vitamins, and a Mediterranean diet. However, other studies do not show a consistent effect. [52]. As literature show regular aerobic exercise favors cognition, dementia risk, and maybe dementia progression [53]. Eight out of 11 studies reported that aerobic exercise interventions resulted in improvement of cognitive capacity. [54]

Secondary prevention includes monitoring of anti-diabetic medication and heart disease drugs, such as cholesterol lowering drugs and antihypertensive drug. [50] Trials with statins given in late life to prevent dementia have been negative, showing no evidence in preventing cognitive decline or dementia [55]. Studies show that diabetic subject treated with combination therapy were associated with less decline in cognitive function. To have in consideration is the association of hypoglycemia and dementia. Not all studies have demonstrated increased risk of dementia in subjects with severe hypoglycemic episodes. Some studies recently have argued that insulin significantly increases the prevalence of dementia and should be avoided, if possible. A documented decrease in the incidence of dementia is seen with the use of oral hypoglycemic agents, such as metformin [56]. Patients treated with medications that increased risk for hypoglycemic episodes have are those in the risk zone.

Data from the Third National Health and Nutrition Examination Survey (NHANES III) show that higher stage of hypertension is associated with worse cognitive performance in ages 70 to 79 and 80 and older, compared with normal BP. Also no significant negative link was seen in older adults aged 60 to 69. On average the elderly subjects who controlled their BP with medication, lifestyle changes or both had the same cognitive performance as subject without hypertension. The controlled hypertension group also had better performance than the group of uncontrolled hypertension. Hinting that with control of BP causes less hypertensive-related cognitive loss in older subjects [32]. Also Treatment of HF patients improved their performance on cognitive tests, suggesting that BP control may be an important
contributor to improve CI [59]. Aggressive lowering of blood pressure in elderly could potentially compromise cerebral perfusion and be harmful in patients with cerebrovascular disease. Evidence is inconsistent regarding the risks of hypotension on dementia, and less is known about the effects of lowering BP in those older than 80 years. Also research on specific regimens are lacking evidence, or research is needed.

Tertiary prevention includes rehabilitation programs after stroke, programs that that facilitate social interactions and activities for an independent daily life. Most stroke rehab programs focus on gaining motor function back. But motor deficits play only a modest role in determining whether the patient can go back to a normal life, while cognitive deficits, principally attention and memory, often limit the patient’s independence more. [8] Functional improvement is usually limited to the particular area practiced and can be lost if maintenance training is not kept up. Brain plasticity basically remains intact into old age. Stroke complications are more common in older and show worse prognosis because of comorbidities such as heart failure and diabetes, and through the patient’s functional limitations—physical, psychosocial and mental. Also Rehabilitation for older is different from the rehabilitation of young patients, as for increased exercise for prevention of stroke it is merely indicated in older, but is actually more effective in older because they have more risk of stroke than younger patients do. The prevention of falls in elderly patients often receives too little attention, focus is on training strength and endurance. Many falls and fractures occur after patients being discharged home even though osteoporosis prophylaxis is given in form of calcium and vitamin D supplementation. This highlights the importance of balance training as well. Better stroke programs for elderly should be established. [78]
METHODS

A comprehensive literature search was performed to detect articles regarding vascular dementia, the risk factors, its relationship with cardiovascular disease and prevention. The search started with a broad literature search in October 2017 on the databases PUBMED/NCBI, ScienceDirect and BMJ journal using the search terms: “vascular dementia”, “dementia”, “cognitive decline”, “hypertension”, “heart failure”, “elderly”, “risk factors”, “cardiovascular disease”, “prevention”.

Articles published before 2007 were excluded as were publications in any other language except for English there were however no geographical exclusions. The search continued until January 2018 and the collected articles were continuously revaluated for their relevance regarding the aim and objective of this paper. For any articles that were deemed eligible the full text was obtained and examined to see if they were relevant or not. Other articles were chosen from the reference lists of the articles already chosen. There were no quality assessments concerning the included studies. A total of 84 references were used in this review.
CONCLUSIONS

1. CVRF such as hypertension, heart failure and diabetes are the most studied and biggest contributors to VaD in elderly.

2. VaD debuts with milder memory deficits and more prominent deficits in executing dysfunction than AD. There is no one criteria for diagnosis leading to delay or under diagnosis of VaD.

3. The most ideal prevention-treatment approach to reduce VaD is considering the wide-range of clinical features and all risk factor on each individual and treat accordingly.
LITERATURE LIST


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