Dementia in Women of the Role of Hypertension and Hypercholesterolemia

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Abstract: Aging is the biggest risk factor in developing dementia and women constitute a larger proportion of older people. It is reported that men can expect to live 2.5–3 years of their remaining life with some form of cognitive impairment and this figure is almost doubled in older women. Gender differences in the incidence of Alzheimer’s disease, vascular dementia, and in the role of vascular risk factors have been reported. In older women, the prevalences of hypertension and hyperlipidemia are significantly higher, as is the likelihood of having multiple vascular risk factors. Early identification of vascular risk factors and optimum management may be a key preventative strategy for development of dementia in women.

The prevalence of hypertension is greater in men than in women until the age of 60, after which hypertension, especially systolic hypertension, is greater in women. Treatment of hypertension may prove to be the key clinical target for long-term intervention with the hope of reducing the risk of dementia. The relationship of cholesterol and its linkage to dementia remains an exciting and conflicting area of research. Studies done on mid-life individuals suggest that early exposure to elevated cholesterol may carry a late-life risk for developing dementia. Women who maintain elevated levels of HDL into old age may be protected against AD.

Conclusion: The conflicting results in the clinical trials on hypertension, cholesterol and dementia call for well-designed, controlled, randomized prospective trials with enough men and women of appropriate age groups to provide adequate power for sex-based analysis.

Kurzfassung: Demenz bei Frauen und die Rolle von Bluthochdruck und Hypercholesterinämie.


Introduction

Dementia is a major medical, social and economic problem that will only worsen with time as the number of older people in the general population increases. Dementia affects 5% of those > 65 years and its prevalence doubles every 5 years [1]. The symptoms of dementia encompass dysfunction of behaviour, function and cognition. As the average life expectancy is greater for women than men, there will be a higher proportion of women in the oldest age group with dementia. It is reported that men can expect to live 2.5–3 years of their remaining life with some form of cognitive impairment (CI) and about 1.5 years of those with dementia [2]. For women, however, these figures rise to 3–4 years with CI, of which 2–2.5 years are affected with dementia. Sex differences in brain aging, for at least some structures, and brain size have been reported. Magnetic imaging studies suggest these changes are more pronounced in men than in women [3]. For instance, men have larger brains but, with aging, may experience atrophy to a greater extent.

There is a growing body of literature on the importance of cardiovascular risk factors such as hypertension and hypercholesterolemia in mid-life and the subsequent development of Alzheimer’s disease (AD), vascular dementia (VaD) and mixed dementia (AD with cerebrovascular disease) [4, 5]. The importance of the role of cerebrovascular disease (CVD) in determining the clinical expression of dementia has also been highlighted, as co-existence of cerebral small vessel disease (lacunar infarcts) with the pathological changes of AD will significantly enhance the clinical expression of dementia [6]. In a 21-year follow-up of a total of 1449 participants (62% women) aged 65–79, people with raised systolic blood pressure (≥ 140 mmHg) or high serum cholesterol concentration (6.5 mmol/L) in mid-life had a significantly higher risk of AD in later life [7]. This result was even after adjusting for age, Body Mass Index, education, vascular events, smoking status, and alcohol consumption.

Sex differences in the incidence of AD, VaD, and vascular risk factors have been reported. In women, the prevalence of hypertension, hyperlipidemia and diabetes are significantly higher, as is the likelihood of multiple vascular risk factors. *Review Criteria: This is a review article based on the best information available. The MEDLINE, Pubmed, and HealthSTAR databases were searched on topics related to dementia in women, and the role of hypertension and hypercholesterolemia in dementia.

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[8]. Moreover, it has been reported that women have a higher rate of silent ischemia and cerebral white matter changes associated with hypertension and diabetes [9, 10]. However, the development of clinical dementia did not vary according to gender in these groups. The Cache County study examined the relationship of gender, cardiovascular risk factors and the risk of developing dementia [11]. The results indicate that gender influences how vascular factors increase the risk of AD and VaD. Obesity increased the risk of AD in females but not in males, while diabetes increased the risk of VaD mainly in females. Similarly, the risk of VaD after stroke was increased significantly more in females. In addition, in a recent study, older women who maintained optimal cognitive function into old age were less likely to have hypertension, diabetes mellitus (DM) or a positive smoking history and those who consumed a moderate amount of alcohol had higher cognitive function [12]. In fact, from EURODEM pooled data it appears that a high level of education is more protective in women than in men [13]. Furthermore, the recent clinical reclassification in dementia diagnosis identifies significantly higher incidence of AD and mixed-type dementia in women in comparison to men (83 vs 16%) [14].

For these reasons, early identification of vascular risk factors and optimum management may be a key preventative strategy for development of dementia in women.

### Blood Pressure and Cognitive Function in Women

The prevalence of hypertension is greater in men than in women until the age of 60, after which hypertension, especially systolic hypertension, is greater in women. In the Framingham cohort, nearly 75% of those over 80 years of age were hypertensive and the majority were women [15].

Longitudinal studies have established hypertension as an independent risk factor for the later development of AD and vascular dementia [16–18]. Treatment of hypertension may prove to be the key clinical target for long-term intervention with the hope of reducing the risk of these common forms of dementia [4]. The mechanism by which hypertension, and possibly other vascular risk factors such as hyperlipidemia, can cause impaired cognition other than through overt cerebral infarction might be inflammation, demyelination or microinfarction in the cerebral white matter [19–21]. Silent cerebral infarctions are a significant mechanism by which hypertension produces brain injury particularly in women [9, 10].

Some observational studies have shown significant reductions in the incidence of dementia in treated hypertensive patients [22, 23]. However, in the 6 randomized controlled hypertension treatment trials that looked at cognition as an endpoint, only 3 showed positive results on cognition [24]. In addition, a recent systematic review found it difficult to make a convincing conclusion on treatment of hypertension and prevention of cognitive impairment and dementia due to considerable heterogeneity between the trials and the fact that a large proportion of the placebo group also received anti-hypertensive treatment [25]. We will review some of these randomized controlled trials (RCT) in more detail. The Study on COgnition and Prognosis in the Elderly (SCOPE) was a prospective antihypertensive trial testing an angiotensin receptor blocker in comparison to placebo [26]. Cognitive decline was not reduced between the two treatment groups. This study targeted a very old population in which the mean age was 76 years and 65% of participants were women. However, there was only a small difference in blood pressure between the two groups as 84% of the placebo group was on active treatment by the end of the trial. Moreover, cognitive function was only assessed with the MMSE (Mini Mental Status Examination) which may not have been sensitive enough to detect any change. These variables may account for the negative outcome of the trial on cognition.

The PROGRESS trial (Perindopril Protection against Recurrent Stroke Study) was a secondary prevention study with antihypertensives in individuals with a history of a stroke or transient ischemic attack [27]. The average age was 64 years and 30% of participants were women. Treatment with perindopril alone did not reduce the risk of stroke but the combined therapy of perindopril with a diuretic (indapamide) reduced the risk of stroke by 43%. Dementia rates were reduced in the combination arm by 34% but only in individuals who had a recurrent stroke during the trial.

The Heart Outcomes Prevention Evaluation (HOPE) trial assessed stroke and cognition as secondary endpoints [28]. This study found a reduction in cognitive decline by 41% in the group on active treatment with ramipril in comparison to placebo. This benefit was only seen in the first 24 hrs in individuals who had a stroke while on treatment and no follow-up data on cognition was reported.

The Syst-Eur (Systolic Hypertension in Europe) study was an antihypertensive trial with 66% female participants that used a long-acting dihydropyridine calcium channel blocker (nifedipine) for the treatment of systolic hypertension [29]. The risk of dementia, which was a secondary endpoint, was reduced by 55% in the active treatment group; however, the incidence of dementia was low in the placebo arm (7 per 1000) which makes the difference between the two groups of questionable significance.

Recent data from the Cache County Study, which is a longitudinal health study on dementia, demonstrated that use of any antihypertensive medication was associated with a lower incidence of Alzheimer’s disease but in particular diuretics and specifically potassium sparing diuretics showed the greatest benefit [30].

### Hypercholesterolemia and Cognitive Function in Women

Total cholesterol (TC) and low-density lipoprotein (LDL) cholesterol increase in men until age 65 years and in women until age 75 years, and then decline. Some epidemiological studies suggest that the intracellular cholesterol transport is involved in the pathogenesis of AD [31]. Cholesterol appears to influence the formation and deposition of amyloid β peptide in the brain which is important in the pathogenesis of AD.
Apolipoprotein E is the main cholesterol transport protein involved in taking cholesterol to the brain. The alleles of apolipoprotein E are associated with an increased risk of AD, and APOE-ε4 alleles cause a two- to threefold increase in the risk of developing AD.

The attributable and the absolute risk associated with an elevated TC and coronary heart disease with increasing age has been well established. The relationship of cholesterol and its linkages to dementia remain an exciting and conflicting area of research. Studies done on mid-life individuals suggest that early exposure to elevated cholesterol may carry a late-life risk for developing dementia.

In a retrospective cohort study of 8845 participants, who were part of a health maintenance study, elevated TC in mid-life (ages 40–45 years) was identified as an independent risk factor for the subsequent development of dementia [32]. In fact those with elevated cholesterol were 42 % more likely to develop dementia. Subtypes of dementia were not identified and only the TC was measured in this study. Women accounted for 54 % of the participants and there was no significant difference between the sexes in the odds of developing dementia. Another prospective longitudinal study has demonstrated an association between mid-life elevated TC and the later development of AD (odds ratio 2.1) [7]. These studies suggest that the neuropathological changes associated with dementia may require a long period of exposure to high levels of cholesterol.

In contrast to the above studies, in a prospective study of older patients with a median age of 75 years, an increase in the onset of dementia with stroke was seen in those individuals with elevated LDL levels but no relationship was seen with Alzheimer’s disease [33]. More recent evidence has also raised controversy to this relationship as it suggests elevated cholesterol in late life may be protective against the risk of dementia. For instance, a prospective study of 392 individuals > 70 years found that increasing cholesterol levels at age 70, 75 and 79 years was associated with a reduced risk of dementia between the ages of 79 and 88 years [34]. The conflicting results may in part be explained by the timing of the cholesterol measurement and its relation to the underlying course of disease rather than when it is measured over the life course. For example, high cholesterol level around ten or more years prior to onset of disease was associated with an increased risk of dementia [35]. This association diminished as the dementia progressed towards clinical onset.

In relation to HDL cholesterol, women who maintain elevated levels of HDL into old age may be protected against AD. The cognitive assessments conducted on 4081 participants 65 years or older in the Women’s Health Study showed that the odds of cognitive impairment declined with increasing levels of HDL [36]. In fact, women with the highest HDL levels had half the risk of becoming cognitively impaired than those with the lowest HDL levels.

Medications such as 3-hydroxy-3-methylglutaryl co-enzyme A reductase inhibitors (statins) are effective for the prevention of secondary cardiovascular and cerebrovascular events in women but their role in primary prevention remains controversial. The role of statins in the prevention of dementia is of increasing interest as statins mechanistically replace Amyloid β 40, resulting in reduced cholesterol and amyloid protein production. In a multicentre, cross-sectional analysis of 23,000 hospital patient records, the relationship between treatment with statins and AD was examined. Patients who received lovastatin or pravastatin, but not simvastatin, had a prevalence of the disease that was 70 % lower than that found in the control group [37]. This observation was also demonstrated in other cross sectional studies. For example, in an observational study of 1037 postmenopausal women, a lower likelihood of AD was associated with the use of statins, particularly in those individuals with higher cholesterol levels [38]. Participants with higher LDL cholesterol levels were more likely to demonstrate cognitive decline. In another retrospective cohort study on the impact of the use of statins on the incidence of dementia, a 60 % reduction in the risk of AD was reported [39]. Of the 655 individuals in this study 74 % were women.

These findings are in contrast to the Cardiovascular Health Study, a cohort of community dwelling seniors 65 years and older, of which ~60 % were women in whom no association between the risk of dementia and the use of statins was found [40]. A recent meta-analysis of 7 independent data sets (4 cohort and 3 case-control) also failed to show beneficial effect of statin use on the risk of dementia or AD [41]. These conflicting results call for a well-designed, controlled, randomized prospective trial.

The PROSPER trial (PROspective Study of Pravastatin in the Elderly at Risk) was a randomized, double-blind prospective study that followed 5804 subjects between the ages of 70 and 82 years, of whom 52 % were women, who had both primary and secondary risk factors for cardiovascular disease [42]. Individuals were randomized to pravastatin or placebo and were followed for the development of CVD (primary endpoint), stroke and dementia (tertiary endpoint). Although there was a reduction in the treatment arm for cardiac events there was no reduction in dementia or stroke rates. However, subjects were only followed for 3 years and since there was no reduction in stroke rates it may not be surprising that there was no effect on dementia. In addition, the study may not have been powered for this tertiary endpoint. Two large-scale ongoing RCTs, the Cholesterol Lowering Agent to Slow Progression of AD study with simvastatin [43], and the Lipitor Effect in AD study, in which 600 patients will be assigned to donepezil plus either atorvastatin or placebo for 72 weeks [44], are designed to determine if the use of statins can slow down the progression of already established mild to moderate AD.

**Conclusion**

The linkage of vascular risk factors to heart disease, stroke and cognitive impairment is particularly important in our approach to the treatment and the prevention along the spectrum of these different diseases. The adverse impact of these health problems will particularly affect women, given the steady proportional rise of the aging population over 75 that will be female. Several factors such as aging, female sex, education and apolipoprotein Eε4 status increase the risk of dementia or AD.
In the design of future prevention studies, there should be inclusion of enough men and women of appropriate age groups to provide adequate power for sex-based analysis. We should not assume similar impact on both men and women from these different risk factors nor should we expect that the treatment effect will be experienced with identical outcomes.

Practical Relevance

- Prevalence of dementia is higher in older women than older men.
- Gender differences in the incidence of Alzheimer’s disease, vascular dementia and mixed type dementia exist.
- In older women, the prevalences of hypertension and hyperlipidemia are significantly higher.
- Women with raised systolic blood pressure (≥140 mmHg) or high serum cholesterol concentration (6.5 mmol/L) in mid-life have a significantly higher risk of dementia in later life.

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