Determinants of cognitive function in old age

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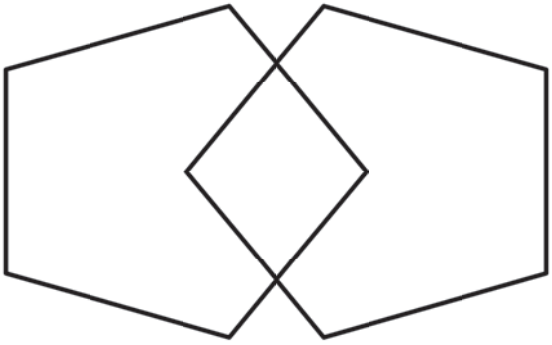
Chapter 1

Introduction



Introduction

The older people get, the bigger the chance of losing cognitive abilities and ultimately to develop dementia. Increasing age is the largest known risk factor of dementia, with a prevalence of 1% in people aged 65-69 years that increases to a prevalence of 29% in people aged over 90 years [1]. Being a strongly debilitating disease that affects large populations, dementia receives attention from both the societal and scientific masses. Despite this undivided attention by many, therapies designed for treating dementia have failed to show high success rates, and a universal pathophysiological mechanism has not been described yet. Classically, late onset dementia is divided in two major forms, Alzheimer's disease and vascular dementia that represent pathological processes that are thought to be different in origin. Alzheimer's disease pathology is characterized by neurofibrillary tangles and neuronal plaques consisting of tau protein and beta-amyloid respectively [2,3]. Vascular dementia on the other hand is characterized as a disorder of vascular origin, with intracerebral ischemic lesions as the hallmark of disease [4,5]. However, over the past decade, general belief has shifted from seeing the two forms as different pathological entities of late onset dementia in the direction of seeing dementia as a mixed pathology syndrome [6,7], with variations in the severity of either pathological form between patients.

Concurrent with this view is that well-known risk factors for cardiovascular disease have also been shown to increase the risk of dementia. Specifically, obesity, hypercholesterolemia, and hypertension at midlife have been associated with an increased risk of late-life dementia [8-13]. Puzzling though is that demented patients have been shown to have lower weight, lower cholesterol levels, and lower blood pressures compared to control subjects [14-17]. Moreover, several studies have shown that, when measured in old age, these risk factors no longer associate with cognitive decline and risk of dementia, and in some studies even associate with better cognitive function and a decreased risk of dementia [18-22]. One of the explanations for the seemingly reversal of the associations of these risk factors with the risk of dementia is the selective survival of study subjects in older populations. This means that those subjects with obesity, hypercholesterolemia, or hypertension in old aged populations may represent a small fraction of all subjects with these risk factors in middle age and therefore represent an exceptional group of subjects that have stayed healthy, despite the presence of these risk factors. Another explanation could be that the values of these risk factors may decline as a result of underlying disease, such as dementia. A third explanation is that higher values of these risk factors could be needed to maintain cognitive function in old age. For instance, a high blood pressure could

be needed to maintain an adequate brain perfusion, due to structural and functional changes in cerebral vasculature with increasing age.

Besides the classical risk factors described above, another risk factor for dementia came to the surface more than a decade ago. The strongest genetic risk factor for dementia as yet is the apolipoprotein E (*APOE*) gene. Carriers of the ε4-allele are at an increased risk of dementia, whereas carriers of the ε2-allele might be protected. The *APOE* gene encodes for the apolipoprotein E (apoE), which has numerous actions, both systemically and intracerebrally. ApoE plays a major role in lipid transportation and cellular uptake of lipids, but has also been shown to play a role in the regulation of inflammatory processes, in the scavenging of lipid peroxidation products, and in the deposition of beta-amyloid plaques in the brain. Although the apoE4 isoform has been shown to have more detrimental effects in these various actions, the exact biological mechanism through which ε4-allele carriers have an increased risk of dementia is not clear yet. As ε4-allele carriers have been shown to have lower circulating apoE levels than ε2- and ε3-allele carriers, variation in plasma apoE levels may play a role in the risk of dementia. Several studies that investigated the association between dementia and plasma apoE levels have shown inconclusive results, with positive, negative and absent associations between plasma apoE levels and dementia [23-27]. An alternative pathophysiological mechanism, for which human data are lacking, is the role that apoE seems to play in neuronal calcium homeostasis. Animal studies have pointed in the direction of apoE facilitating the influx of calcium in neuronal cells [28-33]. As calcium influx has been shown to play a major role in neuronal cell death and apoE4 has been shown to have the strongest effect on calcium influx, this might be another biological explanation for the increased risk of dementia for ε4-allele carriers.

Aim of this thesis

The present thesis aims to clarify the observed reversal of associations of classical risk factors for dementia and mortality with increasing age and to gain insight into the temporal relation of longitudinal changes of these risk factors with cognitive function, underlying disease, and mortality. Another aim is to provide more insight in the biological mechanisms behind the association between both phenotypic and genetic variation in apoE and cognitive function.

Populations under study

Leiden 85-Plus Study

The Leiden 85-Plus Study is a population based prospective follow-up study, which was situated in Leiden, The Netherlands. All citizens of Leiden who reached the age of 85 years between September 1, 1997, and September 1, 1999, were enrolled in the study. Among these 85-year-old persons we initiated a follow-up study to investigate determinants of successful aging. Subjects were visited within one month after the subjects' 85th birthday and annually thereafter for a period of five years. During each visit blood samples were drawn, biometrical measurements were taken, a standardized neuropsychological test battery was performed, and standardized questionnaires regarding health status and functioning were administered. The response rate was 87%; a total of 599 subjects participated.

DOK-Study

The DOK-Study is a family study, which was performed from 2006 to 2007 to investigate midlife factors that associate with an increased risk of late-life Alzheimer's disease. Children from patients with a diagnosis of probable Alzheimer's disease and children from couples of similar age, who were free from dementia, were invited to participate in this study. Because Alzheimer's disease has been shown to have a strong heritability, children from patients with Alzheimer's disease were assumed to be at an increased risk of Alzheimer's disease compared to the children from couples who were free from dementia. In 203 children with a parental history of Alzheimer's disease and 197 children without a parental history of Alzheimer's disease blood samples were drawn, biometrical measurements were taken, and standardized questionnaires regarding health status and functioning were administered.

Memory Outpatient Clinic patients

Between December 1, 1998, and November 29, 2005, a total of 600 patients visited the memory outpatient clinic of the Leiden University Medical Center in Leiden, The Netherlands. All patients who visited the clinic had memory complaints and were examined to a standardized protocol. Patients underwent consultation by a medical doctor and/or a neurologist, who performed a general medical and neurological examination, a standardized neuropsychological test battery was performed, and magnetic resonance images were acquired according to a pre-specified scanning protocol for research purposes.

References

1. Lobo, A, Launer, LJ, Fratiglioni, L, et al. Prevalence of dementia and major subtypes in Europe: A collaborative study of population-based cohorts. Neurologic Diseases in the Elderly Research Group. Neurology. 2000; 54:S4-S9.
2. Jellinger, KA and Bancher, C. Neuropathology of Alzheimer's disease: a critical update. J Neural Transm Suppl. 1998; 54:77-95.
3. Markesbery, WR. Neuropathological criteria for the diagnosis of Alzheimer's disease. Neurobiol Aging. 1997; 18:S13-S19.
4. Kurz, AF. What is vascular dementia? Int J Clin Pract Suppl. 2001;5-8.
5. Jellinger, KA. The pathology of "vascular dementia": a critical update. J Alzheimers Dis. 2008; 14:107-123.
6. de la Torre, JC. Is Alzheimer's disease a neurodegenerative or a vascular disorder? Data, dogma, and dialectics. Lancet Neurol. 2004; 3:184-190.
7. Kudo, T, Imaizumi, K, Tanimukai, H, et al. Are cerebrovascular factors involved in Alzheimer's disease? Neurobiol Aging. 2000; 21:215-224.
8. Kivipelto, M, Ngandu, T, Fratiglioni, L, et al. Obesity and vascular risk factors at midlife and the risk of dementia and Alzheimer disease. Arch Neurol. 2005; 62:1556-1560.
9. Whitmer, RA, Gunderson, EP, Quesenberry, CP, Jr., et al. Body mass index in midlife and risk of Alzheimer disease and vascular dementia. Curr Alzheimer Res. 2007; 4:103-109.
10. Whitmer, RA, Sidney, S, Selby, J, et al. Midlife cardiovascular risk factors and risk of dementia in late life. Neurology. 2005; 64:277-281.
11. Solomon, A, Kareholt, I, Ngandu, T, et al. Serum cholesterol changes after midlife and late-life cognition: twenty-one-year follow-up study. Neurology. 2007; 68:751-756.
12. Launer, LJ, Ross, GW, Petrovitch, H, et al. Midlife blood pressure and dementia: the Honolulu-Asia aging study. Neurobiol Aging. 2000; 21:49-55.
13. Kivipelto, M, Helkala, EL, Laakso, MP, et al. Midlife vascular risk factors and Alzheimer's disease in later life: longitudinal, population based study. BMJ. 2001; 322:1447-1451.
14. Berlinger, WG and Potter, JF. Low Body Mass Index in demented outpatients. J Am Geriatr Soc. 1991; 39:973-978.
15. White, H, Pieper, C, Schmader, K, et al. Weight change in Alzheimer's disease. J Am Geriatr Soc. 1996; 44:265-272.
16. Kuusisto, J, Koivisto, K, Mykkanen, L, et al. Association between features of the insulin resistance syndrome and Alzheimer's disease independently of apolipoprotein E4 phenotype: cross sectional population based study. BMJ. 1997; 315:1045-1049.
17. Guo, Z, Viitanen, M, Fratiglioni, L, et al. Low blood pressure and dementia in elderly people: the Kungsholmen project. BMJ. 1996; 312:805-808.
18. Nourhashemi, F, Deschamps, V, Larrieu, S, et al. Body mass index and incidence of dementia: the PAQUID study. Neurology. 2003; 60:117-119.
19. Li, G, Shofer, JB, Kukull, WA, et al. Serum cholesterol and risk of Alzheimer disease: a community-based cohort study. Neurology. 2005; 65:1045-1050.
20. Mielke, MM, Zandi, PP, Sjogren, M, et al. High total cholesterol levels in late life associated with a reduced risk of dementia. Neurology. 2005; 64:1689-1695.

21. Solfrizzi, V, Panza, F, Colacicco, AM, et al. Vascular risk factors, incidence of MCI, and rates of progression to dementia. Neurology. 2004; 63:1882-1891.

22. Guo, Z, Fratiglioni, L, Winblad, B, et al. Blood pressure and performance on the Mini-Mental State Examination in the very old. Cross-sectional and longitudinal data from the Kungsholmen Project. Am J Epidemiol. 1997; 145:1106-1113.

23. Taddei, K, Clarnette, R, Gandy, SE, et al. Increased plasma apolipoprotein E (apoE) levels in Alzheimer's disease. Neurosci Lett. 1997; 223:29-32.

24. Slooter, AJ, de Knijff, P, Hofman, A, et al. Serum apolipoprotein E level is not increased in Alzheimer's disease: the Rotterdam study. Neurosci Lett. 1998; 248:21-24.

25. Scacchi, R, Gambina, G, Ruggeri, M, et al. Plasma levels of apolipoprotein E and genetic markers in elderly patients with Alzheimer's disease. Neurosci Lett. 1999; 259:33-36.

26. Siest, G, Bertrand, P, Qin, B, et al. Apolipoprotein E polymorphism and serum concentration in Alzheimer's disease in nine European centres: the ApoEurope study. ApoEurope group. Clin Chem Lab Med. 2000; 38:721-730.

27. Folin, M, Baiguera, S, Conconi, MT, et al. Apolipoprotein E as vascular risk factor in neurodegenerative dementia. Int J Mol Med. 2004; 14:609-613.

28. Hartmann, H, Eckert, A, and Muller, WE. Apolipoprotein E and cholesterol affect neuronal calcium signalling: the possible relationship to beta-amyloid neurotoxicity. Biochem Biophys Res Commun. 1994; 200:1185-1192.

29. Wang, XS and Gruenstein, E. Rapid elevation of neuronal cytoplasmic calcium by apolipoprotein E peptide. J Cell Physiol. 1997; 173:73-83.

30. Muller, W, Meske, V, Berlin, K, et al. Apolipoprotein E isoforms increase intracellular Ca2+ differentially through a omega-agatoxin IVa-sensitive Ca2+-channel. Brain Pathol. 1998; 8:641-653.

31. Tolar, M, Keller, JN, Chan, S, et al. Truncated apolipoprotein E (ApoE) causes increased intracellular calcium and may mediate ApoE neurotoxicity. J Neurosci. 1999; 19:7100-7110.

32. Veinbergs, I, Everson, A, Sagara, Y, et al. Neurotoxic effects of apolipoprotein E4 are mediated via dysregulation of calcium homeostasis. J Neurosci Res. 2002; 67:379-387.

33. Qiu, Z, Crutcher, KA, Hyman, BT, et al. ApoE isoforms affect neuronal N-methyl-D-aspartate calcium responses and toxicity via receptor-mediated processes. Neuroscience. 2003; 122:291-303.