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The epidemiologic study of dementia: a life-long quest?

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Abstract

Based on many experimental and observational studies we now understand that neurodegenerative brain changes begin by middle age. Characteristics of the risk factors for these brain changes may also change with age. A review is conducted of studies that report on the association of mid-life risk factors to late cognitive impairment and dementia. Issues related to the interpretation of the data are discussed. The studies suggest that mid-life cardiovascular risk factors, and in particular elevated levels of blood pressure, increase the risk for late-life cognitive impairment and dementia. Our understanding the contribution of cardiovascular risk factors to late age brain disease has been helped tremendously by prospective studies with long follow-up. To better understand which risk factors lead to disease initiation, progression and prognosis, a life course approach to the epidemiologic study of dementia is needed.

Keywords: Epidemiologic study; Apolipoprotein E ε4 allele; Neurodegenerative brain

We are slowly moving back the bar on diseases of old age, as we understand that disease processes that are 'age-related' begin long before they are clinically evident. Studies, reviewed below, suggest that by the age most clinical and epidemiologic studies of brain aging begin, i.e., 65-years-old, individuals have already experienced the initial pathologic changes that lead to a degeneration in brain structure and function. On the exposure side, there is a growing body of evidence documenting age-related changes that may directly or indirectly affect, or be affected by, neurodegenerative processes. The result is that the relationship between a risk factor and late-age brain pathology may differ depending on the age the risk factor is measured relative to the outcome. This can have important implications for the selection and timing of prevention and treatment strategies. This review of specific risk factors measured in middle and late-age will illustrate this point. The aim is to develop a framework for taking a life course approach to the study of risk factors for late age cognitive impairment and dementia.

1. Changes with age

1.1. Brain structure and function

Studies conducted at different ages suggest brain aging begins relatively early. From the studies of Braak et al. [2], we have learned that the classical markers of Alzheimer's disease pathology can start to appear in autopsied brains of 40-year-olds. White matter hyperintensities appear on magnetic resonance images (MRI) of the brains of middle-age adults without a history of cerebrovascular disease [24]. Cross-sectional MRI studies show that selected sub-regions of the hippocampus also begin to atrophy at this age [47]. The density of the frontal cortex gray matter may begin to decrease at an even earlier age [48]. These anatomical changes may be markers of cellular and neurochemical processes that are the basis of age-associated decline in specific domains of cognitive function [36]. Relatively early changes in frontal lobe functions, in particular, have been documented in longitudinal studies [42].

2. Risk factors

The levels of risk factors, such as a blood pressure or cholesterol level, also change with age, as a result of alter-

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ations in brain and peripheral structures, in gene expression, and in the nature of endogeneous and exogenous environmental exposures.

2.1. Genetic risk factors

With the increase in our ability to study the genetic contribution to diseases in old age, comes the understanding that the role of genes and their proteins may change with age. The genetic changes can work by turning on or off different neuroprotective or neurotoxic pathways. Although there are many studies in which the gene expression in developing organisms is compared to that in matured organisms, there are few studies comparing gene expression in young adults and older adults. Based on one recent study it was estimated that 6.2% of genes had different expression patterns in older compared to young adults. The differences were in the range of 1.4–1.9 times different. Of those genes that could be characterized, the greatest proportion was involved in regulating DNA and RNA metabolism [25].

In addition to gene expression changing with age, selective mortality or preservation of certain genotypes may introduce changes in the gene pool of susceptibles that live to the age when the incidence of disorders of cognition increases [54]. For instance, one study suggests that people who smoke and have an apolipoprotein E ε4 allele (APO E ε4) are at increased risk for early cardiovascular-related mortality [18] compared to non-smokers with an ε4 allele. Such a pattern would deplete the pool of smokers who were genetically susceptible to AD because they carried the apolipoprotein E ε4 allele. In practice, this would lead to a higher estimated risk for AD associated with smoking in people with no ε4 allele compared to those with a ε4 allele. Such a differential in risk has been reported. In the Rotterdam Study, for example, smoking was a strong risk factor for AD in individuals without the APO E ε4 allele (odds ratio = 4.6), but had no effect in participants with this allele (OR = 0.6) [33]. This is illustrated in Fig. 1, which shows, due to the selective mortality pattern, the smokers that survive to old age have a low genetic risk. The remaining smokers with the apolipoprotein E ε4 allele may be more resistant (for genetic reasons) to neurodegenerative changes.

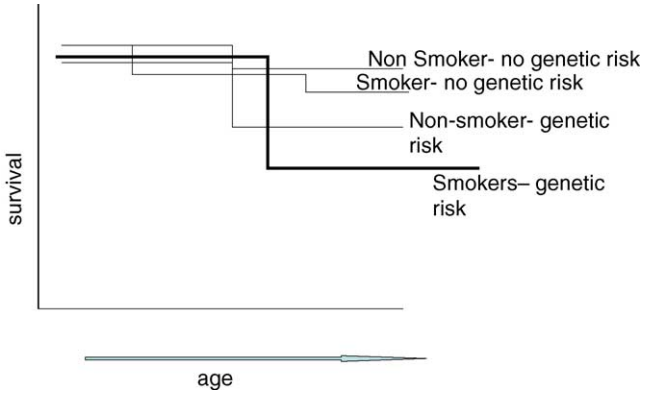

Fig. 1. Survival of smokers with and without a genetic risk for Alzheimer's disease. Based on findings from [18].

2.2. Environmental risk factors

Age-associated changes in gene expression can be modified by factors in the environment. The impact of environmental factors, such as smoking, diet, physical activity and vascular disease, can be expected to change over time both within an individual and across birth cohorts [19]. Cardiovascular risk factors, such as hypertension, hypercholesterolemia and diabetes increase in prevalence by middle age, although by old age, these risk factors may decline in prevalence [1,14,26]. Within any time period, rates of smoking decrease with age and are usually lower for women than men [37]. There are also secular trends in smoking and other cardiovascular risk factors. For instance, over time the prevalence of obesity and diabetes in the population has increased, physical activity [49] and smoking has decreased, and treatment for conditions such as high blood pressure has increased. Such trends can be expected to change survivorship, and the incidence and co-occurrence of chronic diseases such as diabetes and stroke. Even the role of education may change over time. The generation of older persons now participating in studies of aging, did not have compulsory schooling as children do now.

In addition to change in the external environment there are also endogeneous changes with age. One part of this change is in the hypothalamus–pituitary–adrenal axis (HPA) system, which plays a central role in many of the autonomic, behavioral, and endocrine systems that are hypothesized to modify the risk for dementia [31,52]. Specifically, the HPA plays a direct or indirect role in regulating risk factors such as blood pressure, cholesterol, the stress response, inflammatory response, sex hormones, and weight. Many studies have documented changes with age in endocrine levels and in the response to feedback loops that regulate the levels [12,16]. Both peripheral and central systems could lead to a change in the HPA. Conditions often co-morbid with dementia, such as diabetes, stroke or depression may also modify function of the HPA. There is also pathologic evidence that the HPA may start to atrophy in middle age [41], a pattern that may reflect a direct neurodegenerative process.

3. Long-term perspectives on the study of dementia: mid-life risk factors and the risk for late-life disorders of cognition

These age-related changes in brain structure and function, and concurrent changes in risk factors for cognitive impairment may be dependent or independent and various scientific approaches are needed to determine how such changes are related. One important approach is prospective population-based studies that measure cognitive function in late age—and risk factors in early and middle age, when pre-

sumably risk factors are less affected by the disease. The value of prospective studies of dementia with a long follow-up is illustrated in this brief overview. The association is examined between risk factors measured in mid-life (for the purposes of this review mid-life is 40–60 years of age) and the risk for late-age (i.e., after 65 years of age) cognitive impairment, dementia and specific measures of brain pathology, hereafter referred to as diseases of cognition (DOC). In this context, examples will be provided to demonstrate how the interpretation of an association between a risk factor and diseases of cognition can change depending on how early in the disease process the risk factor is measured.

3.1. Epidemiologic studies of mid-life risk factors and late-life disorders of cognition

Several population-based cohorts of middle-aged men and women, started in the 1960s and 1970s, have been examined through to late age, often accumulating more than 20 years of follow up. Many of these studies have one or more measure of brain function and structure including cognitive function, MRI, clinical diagnoses of dementia, and neuropathology. Such studies include European cohorts developed from the World Organization's MONICA studies [29,43] and in Finland [21], Iceland [45], and the Netherlands [7]; in the United States [Japanese–American men [29], NHLBI Veterans twin study [3], and the Framingham study [9]]; and in Japan [53]. Many of these cohorts were started in response to the epidemic of cardiovascular disease that afflicted European and North American countries in the late 1950s and 1960s. As a result we know the most about the association of these factors to the risk for DOC. Because relatively standard measures of cardiovascular disease and risk factors were employed in these studies we also have the opportunity to compare results across cohorts.

3.2. Blood pressure

The increase in the risk for late-life disorders of cognition associated with elevated mid-life levels of blood pressure is the most consistent finding across cohorts. The elevated risk has been estimated for cognitive impairment [3,9,27], dementia including Alzheimer's disease [22,28], MRI findings of brain atrophy and white matter lesions [4,6,7,17], and neuropathologic markers of AD [38]. Untreated mid-life hypertension may be more strongly related to the risk for cognitive impairment in men with the APO E ε4 allele [34].

There are few risk factors that have been studied in so many cohorts, and in multiple measures of brain aging. However, not all studies support these findings—the results of early studies (i.e., [11]), and even more recent ones [32] did not find an increasing level of blood pressure was a risk factor for DOC. In fact, cross-sectional analyses in particular, suggest elevated levels of BP protect against dementia [15]. Closer analysis of the inconsistencies between cross-sectional and longitudinal studies suggests the discrepancies among them can be accounted for by elements of the study design, specifically a combination of the duration of time between the measurement of blood pressure and brain function, and the ages at which the measurements were made.

In general, the older the age the blood pressure is measured and the shorter the interval between the measure of blood pressure and brain function the more difficult it is to validly investigate whether the risk for DOC is altered by levels of blood pressure. The reason for this is that blood pressure declines with 'age' or more specifically—with pathology. For instance, the studies of Skoog et al. [46] show that, compared to non-demented persons, those who were eventually diagnosed with dementia, experienced a greater decline in blood pressure over the 15 years prior to the diagnosis of dementia.

There are many reasons for the decline in blood pressure, including vessel stiffening [26] and weight loss. Some of these changes in blood pressure may be the indirect result of diseases such as stroke or diabetes [23]. It is also possible that changes in the autonomic regulation of blood flow [40] leads to a decline in measured BP. Such changes may also result from neurodegeneration.

3.3. Cholesterol

Multiple studies have examined the association of mid-life cholesterol levels to DOC. In settings such as Finland, where very high levels of cholesterol are characteristic of the population, a positive association between total cholesterol level and late-life cognitive impairment [21] and dementia [22] has been reported. However, these findings have not been replicated in other cohorts [50]. In the cohort of male twins [4], low HDL was associated with an increased risk for white matter lesions; in a cohort of Japanese–American men, high HDL was associated with an increased risk for neuropathologic markers of AD [30].

Unlike blood pressure, there is no consistent relationship of the interval between cholesterol measure and cognition and the strength of the association. More basic research is needed to understand the role of cholesterol and lipoproteins in brain aging. In addition, there are questions about the interpretation of the epidemiologic association that need to be raised. Many studies have demonstrated that cholesterol levels are lower in persons with certain medical conditions [10] including occult illness such as cancer, inflammation, weight loss or change in diet that might follow events such as myocardial infarction. This means the group with low cholesterol – which is thought to be the 'optimal' reference – includes a sub-group of individuals who are sick and have not had 'life-long' exposure to low levels of cholesterol. Therefore, part of the reason for the inconsistencies among studies may be due to differences among cohorts in the prevalence of other co-morbidities that might affect cholesterol levels. A 'contaminated' reference group can reduce the power of the analysis, or bias the estimation and the comparisons of risk among studies to the extent they differ in the prevalence of conditions causing cholesterol levels to decline. Other fac-

tors, such as treatment patterns should also be considered when comparing results across cohorts.

3.4. Other risk factors

Other mid-life cardiovascular risk factors that have been reported to increase the risk for disorders of cognition include: smoking [13,51], poor lung function [3,5], indicators of glucose dysregulation [3,20], and atherosclerosis [8]. Glucose dysregulation may be more strongly related to the risk for cognitive impairment in men with the APO E ε4 allele [3,35].

The association of DOC to these various cardiovascular risk factors suggests there may be some common mechanisms mediating these relationships. Inflammation is one such mechanism that has been investigated both in experimental studies and epidemiologic studies of risk factors for cardiovascular disease [39]. The association of mid-life markers of inflammation and the risk for late-age dementia has been examined in the Honolulu Asia Aging Study [44]. In this study raised levels of C-reactive protein (CRP), a marker of an inflammatory response, were associated with an increased risk for diabetes, stroke, blood pressure, and history of smoking. Increasing levels of CRP also increased the risk for Alzheimer's disease with no cardiovascular disease contributing to the dementia, Alzheimer's disease with contributing cardiovascular disease, and vascular dementia. The risk estimates were moderately reduced after controlling for cardiovascular risk factors, suggesting these factors partially explain the association of mid-life CRP and late-life dementia. However, the relationship was not completely explained by these risk factors. Better measures of cardiovascular risk factors will be needed to understand how inflammation and cardiovascular risk factors interact to affect the brain. Other mechanisms may also explain the association. Possibly, there is leakage from the brain to the periphery of cytokines produced in reaction to already existing cerebrovascular lesions. Further people with high levels of CRP may have a genetic tendency towards an overactive immune system that increases the risk for several different chronic diseases, including DOC.

4. Lessons about diseases of cognition from the long-term follow-up studies

The body of research reviewed here suggests mid-life levels of cardiovascular risk factors, and in particular elevated levels of blood pressure, increase the risk for DOC that emerge 20 years or more after the risk factor is measured. There is some support for the hypothesis that increased genetic susceptibility, marked by having the apolipoprotein E ε4 allele, may interact with these risk factors to increase the risk for DOC. Chronic inflammation may also contribute to an increased risk for DOC, either directly or indirectly through other cardiovascular risk factors.

Our understanding of the direction and magnitude of the association between diseases of cognition and cardiovascular risk factors has been helped tremendously by these long-term prospective studies. We now understand better that by mid-life we already can detect changes in the brain that are predictive of dementia. We also have data showing risk factors of interest change, either as a direct, indirect or unrelated consequence of neurodegeneration. Thus, when we measure particular risk factors will certainly dictate to a large extent the direction and magnitude of their relationship to DOC.

These findings have important implications for prevention and treatment of the disease-in particular the timing and nature of the intervention. The blood pressure findings provide an illustrative example (Fig. 2). The mid-life studies suggest treatment of high blood pressure will contribute to a reduction in risk for DOC; the cross-sectional studies [15] suggest elevated levels of blood pressure should not be treated. Because of such inconsistencies in the literature, the aggressive treatment of high blood pressure, or any treatment of blood

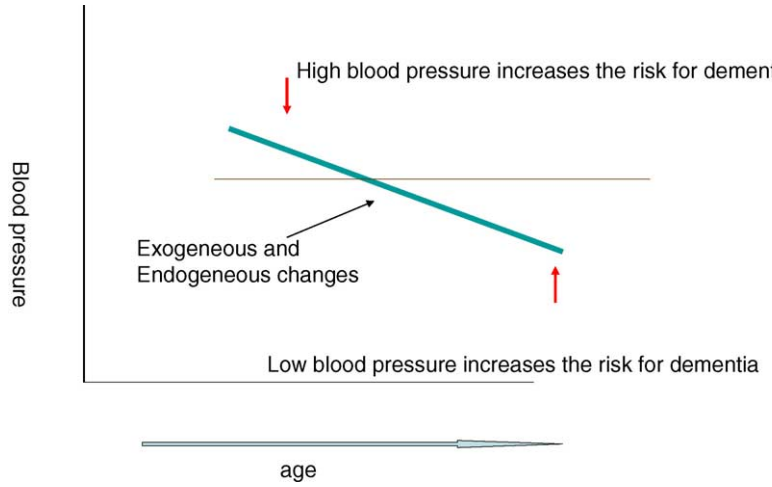

Fig. 2. Change in the relation of blood pressure to risk for dementia as people age and the interval increases between the measurement of blood pressure and the onset of dementia.

of blood pressure in older persons remains controversial [14].

The findings also inform us on new directions for defining phenotypes in epidemiologic research in dementia. Because most DOC increase dramatically in incidence only after 75 years of age, new approaches will have to be found to characterize a phenotype based on characteristics of a person when they are younger. More research will be needed on 'surrogate' markers of DOC that can be measured when individuals are younger and that are predictive of late age DOC. This life course approach will help identify factors that may initiate the disease process, contribute to its progression and the prognosis once the clinical threshold of dementia is crossed. It will also provide information on the different trajectories to health and disease in old age.

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