Vascular Risk Factors and the Risk of Parkinson's Disease: Some New Findings

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Parkinson's disease (PD) is the second most common neurodegenerative disease of the elderly.[1] PD is a debilitating disorder manifested by bradykinesia, resting tremor, muscular rigidity, gait disturbances, and postural reflex impairment.[1] The underlying pathologic lesion is the loss of the pigmented neurons of the substantia nigra, and selected brain stem dopaminergic cell groups. However, the causes of PD are not well known. The loss of substantia nigra neurons results in depletion of the neurotransmitter dopamine in these areas. There is evidence that genetic factors play a key role in an early-onset PD.[2,3] Studies of twins have provided strong evidence for an important role of environmental factors in the etiology of typical PD.[2] The development of PD involves an interaction between genes and environmental factors.[2] Thus, its prevention is likely to be at least partly possible. In order to determine interventions that would prevent or delay the onset of PD, modifiable risk factors for the disease have to be identified first. These risk factors could then be used as targets for intervention, and also population-based health education and intervention programs could be developed. Vascular risk factors, such as hypertension, dyslipidemia, and type 2 diabetes, are major risk factors for coronary heart disease (CHD) and maybe also for stroke. In recent years, several prospective studies have assessed the association of vascular risk factors and the risk of PD. In this review, we summarize current results about the role of vascular risk factors in the development of PD risk.

Obesity and PD Risk in Prospective Epidemiological Studies

Obesity is a major public health problem worldwide.[4] Excess body mass is not only associated with a number of health-related risk factors, but also seems to be an independent risk factor for CHD, type 2 diabetes, and several types of cancers.[4] In recent years, only a few prospective studies have assessed the association between obesity and the risk of PD, and the results are inconsistent.[5-8] The first report from Honolulu Heart Program indicated that greater midlife triceps skinfold thickness was associated with a higher future risk of PD.[5] However, the results from 3 other studies, the Health Professionals Follow-up Study, the Nurses' Health Study, and Harvard Alumni Health Study, did not support a role of overall obesity in PD pathogenesis.[6,7] The analyses from FINRISK study found that excess weight, defined as a body mass index (BMI) of 23 or more, was associated with an elevated risk of PD.[8]

Abdominal obesity (measured by waist circumference or waist-to-hip ratio) as a central factor in the metabolic syndrome has been shown to be more closely associated with the risk of type 2 diabetes, CHD and stroke than overall obesity (measured by BMI) and the increased risk appears to be independent of overall obesity.[9-12] However, the association of abdominal obesity with the risk of PD has not been fully studied and more studies are needed.

Blood pressure and PD Risk in Prospective Epidemiological Studies

High blood pressure is one of the most important risk factors for CHD and stroke in all ethnic groups.[13-15] The association between blood pressure and CHD and stroke mortality is strong and direct, and the absolute risk of CHD and stroke mortality associated with high blood pressure increases with age.[15] High blood pressure is associated with an increased risk of dementia/Alzheimer's disease.[16,17] Until now, no studies have determined if there are dose-response associations of systolic and diastolic blood pressure with PD risk since few available prospective studies have measured blood pressure at baseline. One recent analysis from the Nurses' Health Study and the Health Professionals Follow-up Study found that PD risk was not significantly related to self-reported history of hypertension (relative risk 0.96; 95% confidence interval 0.80-1.15).[18] In another case-control analysis, long-term use of calcium channel blockers was associated with a significantly reduced risk of PD, while the risk was not materially altered for users of angiotensin converting enzyme inhibitors or beta-blockers and for users of angiotensin II antagonists.[19] However, potential bias could be substantial in this case-control study. Data from larger cohort studies with available information of blood pressure and antihypertensive treatment are needed to clarify the role of blood pressure on the development of PD.

Serum Lipids Levels and PD Risk in Prospective Epidemiological Studies

It is well known that high serum total cholesterol levels correlate positively with an increased risk of CHD.[20,21]

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However, the association between serum total cholesterol level and the risk of neurodegenerative diseases has been debated. Some prospective studies have found that high serum total cholesterol may increase the risks of dementia/Alz and ischemic stroke.[20] Other studies have found no association[24] or an inverse association between serum total cholesterol and the risk of hemorrhagic stroke.[20] In addition, little is known about the association between serum total cholesterol and the risk of PD. Until now, only a few case-control studies[25-28] and five prospective epidemiological studies[18,29-31] have examined the association between serum total cholesterol or a history of hypercholesterolemia and the risk of PD, but the results are inconsistent. An inverse association has been found in one prospective study (the Rotterdam study),[30] however, no significant association was reported in the case-control studies[25-28] and one prospective study (the Honolulu Heart Program).[29] Most of these studies were either case-control studies[25-28] or prospective studies with very few PD cases (less than 100 cases) during follow-up.[29,30] With the pooled data from the Health Professionals Follow-up Study and the Nurses' Health Study, PD risk increased non-significantly with a baseline history of physician-diagnosed high cholesterol (relative risk 1.29, 95% CI 0.98-1.69).[18] Recently, we evaluated prospectively the association between serum total cholesterol and the risk of incident PD among 24,773 Finnish men and 26,153 women of 25 to 74 years of age without a history of PD and stroke at baseline.[31] Serum total cholesterol was measured at baseline survey. During a mean follow up period of 18.1 years, 321 men and 304 women developed incident PD. The multivariable-adjusted (age, study year, body mass index, systolic blood pressure, education, leisure time physical activity, smoking, alcohol drinking, coffee and tea drinking, cholesterol-lowering agent use, and the history of diabetes) hazard ratios of incident PD at different levels of total cholesterol (<5, 5-5.9, 6-6.9, and ≥7 mmol/l) were 1.00, 1.33, 1.53, and 1.84 (P for trend = 0.035) in men, 1.00, 1.55, 1.57, and 1.86 (P for trend = 0.113) in women, and 1.00, 1.42, 1.56, and 1.86 (P for trend = 0.002) in men and women combined (adjusted also for sex)

Despite the inconsistent or weak association of serum total cholesterol with PD and stoke, the effect of lowering cholesterol concentrations with statins on reducing the risk of stroke has been reported in recent clinical trials.[32,33] However, this effect seems to be associated with the extent of low-density lipoprotein (LDL) cholesterol reduction.[32,33] It is well known that total cholesterol includes high-density lipoprotein (HDL) cholesterol, LDL cholesterol and triglycerides. A recent review has recommended statin therapy as the most important advance in stroke prevention since the introduction of aspirin and antihypertensive treatments.[33] In 2001, the National Cholesterol Education Program (NCEP) Adult Treatment Panel III Guideline also continued to identify elevated LDL cholesterol as the primary target of cholesterol-lowering therapy for primary and secondary prevention of CHD.[32] Thus, it is important to understand the association of other serum lipids levels, such as LDL cholesterol, HDL cholesterol and triglycerides, and use of lipid-lowering drugs with PD risk, however, the epidemiologic studies on this aspect are sparse. A systematic review has demonstrated that the apolipoprotein E (APOE) ε2 allele is positively associated with higher prevalence of PD.[34] Furthermore, the APOE ε2 has been consistently associated with lower serum LDL cholesterol.[35] Recently, lower concentrations of LDL cholesterol have been reported to be associated with higher occurrence of PD in a case-control study; however, serum HDL cholesterol did not differ significantly between PD patients and controls.[28] In an updated analysis from the Honolulu Heart Program, an inverse association between LDL cholesterol and PD risk was presented among 3233 subjects with 41 PD cases.[36] No association between serum HDL cholesterol and PD risk was found in the Rotterdam study.[30] The case-control study design and very few PD cases in prospective studies limited the results in above studies.[28,30,36] Therefore, large epidemiologic prospective studies are needed to further evaluate the association of different types of serum lipids and use of lipid-lowering drugs with the development of PD.

Hyperglycemia/Diabetes and PD Risk in Prospective Epidemiological Studies

Type 2 diabetes is one of the fastest growing public health problems worldwide,[37] and is associated with multiple complications. Evidence from prospective epidemiological studies has identified type 2 diabetes as an independent risk factor for multiple hyperglycemia-induced complications virtually in all organs, including neurodegenerative diseases such as diabetic neuropathy,[38] stroke,[39-42] dementia,[43-45] and Alzheimer's disease.[43-45] However, little is known about the association between diabetes and PD risk. Previous results on the association between diabetes and PD came from a few cross-sectional studies or case-control studies.[27,46-48] Only recently, the data from our study[49] and the Physicians' Health Study[50] indicated that a history of type 2 diabetes was associated with an increased risk of PD, however, the Nurses' Health Study and the Health Professionals Follow-up Study did not support this finding.[18] In all of these four studies, type 2 diabetes was diagnosed based on self-report or hospital-discharge register.[18,49,50] In the elderly, the true prevalence of diabetes is over 30%, and more than half of them are asymptomatic and undiagnosed.[51,52] In addition, more than 30% have impaired glucose tolerance, which makes more than half of elderly people affected with hyperglycemia.[51,52] Most of the elderly hyperglycemic subjects can only be found by an oral glucose tolerance test (OGTT). The importance of hyperglycemia including impaired glucose tolerance and asymptomatic/undiagnosed diabetes on the development of PD, however, has not been estimated in the previous studies since most of them have not carried out an OGTT or a fasting glucose test.

In conclusion, the association between vascular risk factors and the risk of PD has been assessed by several prospective studies in recent years, but the results are inconsistent. Further studies are needed to clarify the causality.

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