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The Effect of Statins on Vascular Cognitive Impairment

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Vascular cognitive impairment (VCI) is an umbrella term of all forms of cognitive disorders associated with cerebrovascular diseases. VCI is potentially preventable by rigorous identification and treatment of cerebrovascular disease risk factors and symptomatic improvement with statins. The use of statins are not only lower serum cholesterol levels, but also inhibit pivotal enzymatic reactions that lead to amyloid deposition and plaque formation. **Vascular Neurology 2018;6:12-14**

Key Words Vascular cognitive impairment, Vascular risk factor, Dementia, Alzheimer's disease, Statin.

Introduction

As the number of aged people are growing in each year and the prevalence of dementia is also increasing. Korea is moving fast from an aged society to super-aged society which represents the percentage of population 65+ years old will more than 20 percentages.[1] The prevalence of VCI is strongly related with age, between 65 to 84 years old age has the higher prevalence in the vascular dementia (VaD) than other age groups. VCI represents a broad concept that contains the full spectrum from vascular mild cognitive impairment (vascular MCI) to VaD. VCI includes the case with mixed pathologies such as mixed vascular and Alzheimer's disease type pathologies. VCI also refers to all forms of cognitive impairment associated with cerebrovascular diseases, regardless of underlying mechanism such as multiple or single territorial or small infarcts and irrespective of the occurrence of stroke symptoms. Human brain composed of approximately 25% of total cholesterol in the body, and cholesterol is vital element to normal brain functioning that includes learning and memory.[2] The cholesterol plays an important role in the body such as major components of myelin sheath, membrane lipid in neuron and astrocyte, regulation of ion channel permeability, signal transduction, and other cellular functions. However, high cholesterol levels link to increased amyloid-β generation and deposition.[3] Previous study represents that statins are effective in lowering lipprotein-cholesterol (LDL-C) which reduce the risk of atherosclerotic CVD. Statins increase the high-density lipoprotein-cholesterol (HDL-C) and decrease triglycerides (TG)[4] and also exert anti-inflammatory effects in the brain. The statins' pleiotropic effects include antiproliferative and antithrombotic benefit and endothelial dysfunction improvement.[5] The healthy brain depends on the normal network of blood vessels in our body for optimal functioning. When the brain has restricted blood flow, the brain cells could die and the brain function deficit happen.[6] The cognitive function such as thinking functions of the brain including language, attention, reasoning, and memory is affected by cerebrovascular disease. VCI is consisted of a variety of conditions which implicates the different types, locations, and extension of the underlying cerebrovascular diseases and brain damage. The definition of VCI is "a syndrome with evidence of clinical stroke or subclinical vascular brain injury and cognitive impairment affecting at least one cognitive domain".[7] VCI includes the contribution of the cerebrovascular disease to cognitive impairment in the presence of additional brain disease such as Alzheimer's disease. The most serious form of VCI is the vascular dementia (VaD) which associated with the significant cognitive decline to disturb the daily activities.8 The construct of multi-infarct dementia, by attributing cognitive impairment to multiple stroke, allows the prevention of cognitive impairment by controlling risk factors for stroke such as hypertension, diabetes, smoking, and dyslipidemia. We suggest that the usage of statin may beneficial to VCI.

Vascular Risk Factor

The brain relies on the constant blood supply to deliver essential nutrients and oxygen to support its own function. The

neurovascular unit which consists of vascular, perivascular, and brain cells work together to assure adequate blood perfusion to the brain and maintain the homeostasis of the brain's internal milieu.[9] Hypertension (HTN) and dyslipidemia belong to the most prevalent modifiable risk factors for cerebrovascular and cardiovascular diseases. The World Health Organization (WHO) has set a global goal to 25% reduction of prevalence of HTN by 2025 to reduce the risk of cognitive decline. HTN is the major vascular risk factor of cognitive impairment.[1,7] The brain is a major target of end-organ damage in HTN. HTN has profound effects on the cerebral vasculature leading to both structural and functional alterations affecting the neurovascular unit at all levels of the cerebrovascular tree.[10] These alterations may promote vascular insufficiency, leading to neuronal dysfunction and cognitive impairment.[11] HTN cause the damage of cerebral tissues which result in leukoaariosis or lesion in the preventricular and subcortical white matter regions.[12] The mild cognitive impairment patient has a reduced cerebral blood flow (CBF) and cerebrovascular reactivity.[13] The cerebral hypoperfusion with accelerated cognitive decline and an increased risk of dementia in the general population.[14] Brain cholesterol contributes to development of synapse and formation, dendrite differentiation, axonal elongation, and long-term potentiation.[15] However, hypercholesterolemia is a highly prevalent, modifiable risk factor for vascular diseases. Especially elevated LDL-C is central to the development and progression of atherosclerosis.[16] Many previous population-based studies demonstrate that hyperlipidemia in hypercholesterolemia is associated with the occurrence of cognitive impairment in middle age.[17] High cholesterol is often a prerequisite for atherosclerotic plaque formation.[18] HDL-C may involve in the removal of excess cholesterol from the brain mediated by apolipoprotein E (ApoE) and heparin sulfate proteoglycans in the subendothelial space of cerebral microvessels. ApoE is an important protein involved in cerebral cholesterol transport and influences aggregation and clearance of Aβ peptide.[19] In addition, HDL particles reverse the inhibitory effect of oxLDL particles on endothelium-dependent arterial relaxation and inhibit cytokine-induced expression of endothelial cell adhesion molecules.[20] Otherwise, diabetes mellitus is associated with cognitive decline and increase the risk of dementia.[21] The insulin signaling has important role in brain physiology and cognition,[22] but the excessive glycosylation alters the blood brain barrier.[23] Microcirculation defined as lessen than <150 μm arterioles, capillaries, and venules to deliver the nutrients and waste production to stabilized hydrostatic pressure at the level of capillaries.[24] Previous study represented that diabetes is associated with brain abnormalities[25] especially in small and large blood vessels to cause the retinopathy, nephropathy, cardiovascular diseases, and cerebrovascular diseases.[26,27]

Statin Use and VCI

Statins are the drug that inhibit 3-hydroxy-3-methyglutaryl coenzyme A (HMG-CoA) reductase. It is the first-line drug therapy for the treatment of hypercholesterolemia and the first choice for the preventive cardiovascular diseases.[28] HMG-CoA reductase is the rate-limiting enzyme in the cascade of cellular cholesterol biosynthesis. The statins (atorvastatin, fluvastatin, lovastatin, pitastatin, pravastatin, rosuvastatin, and simvastatin) reduce formation and entry of LDL cholesterol into the circulation and upregulate LDL receptor activity by lowering LDL-C, TG, and increasing HDL-C.[29] Statin may affect cognition through their effect on the level of cholesterol. LDL-C and low level of HDL-C are known risk factor for carotid atherosclerosis and coronary artery disease,[30] which may cause the cognitive impairment secondary to cerebral hypoperfusion or embolism.[31,32] Dementia has been proposed to be caused by large vessel disease and microvascular damages. An effective therapy for the VCI management may related to resolve the hypoperfusion and provide the therapeutic improvement of cerebrovascular function.[33] The early identification and management of atherogenic risk factor might be essential to alleviate the VCI signs and symptoms.[34] Controlling the key atherosclerotic stroke risk factors such as hypertension, diabetes mellitus, and dyslipidemia provide the possibility of preventing VCI.[35] Numerous previous studies have demonstrated the beneficial effects of statins on endothelial dysfunction and chronic inflammation.[36] Statins have beneficial effect on the microvasculature which includes endothelial nitric oxide synthase (eNOS)[37] and reducing endothelin-1,[38] thereby dilating capillaries and increasing blood flow. In Alzheimer's disease cerebral perfusion is decreased in affected areas of brain,[39] capillary endothelium shows pathologic changes,[40] and eNOS is decreased in capillaries in the brains.[41] The effect of statins in reducing the risk for dementia may involve such beneficial effects on the cerebral capillary endothelium or other properties of the drugs.

Conclusion

The growth of aging population, the prevention and treatment of the cognitive impairment and dementia is emphasized. Numerous previous studies have supported the hypothesis of statin are effective in reversible short-term cognitive impairment and decrease the risk of dementia. Management of modifiable cardiovascular risk factors such as hypertension, diabetes, and hypercholesterolemia may significantly reduce the chance to developing dementia. The associations between plasma lipids and cognition and the underlying mechanism, the relationship between statins and cognitive function are complex and currently not yet fully understood. However, statins have important benefits in patients with high risk of cardiovascular and cerebrovascular events.

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