A new dawn of preventing dementia by preventing cerebrovascular diseases

Yuesong Pan and colleagues discuss the relation between cerebrovascular diseases and impairment of cognition, with an emphasis on a chance to prevent dementia by preventing cerebrovascular diseases

Cerebrovascular diseases and dementia are two leading contributors to impairment of brain health and neurological disability in older people.[1] The prevalence of these two neurological disorders has increased in recent years as the population has aged and grown. Globally, an estimated 42.4 million cases of stroke occurred in 2015,[2] and approximately 50 million cases of dementia (including Alzheimer's disease, vascular dementia, and other dementias) occurred in 2018.[3] Strategies for preventing and treating stroke have progressed substantially in recent years, but no effective treatment yet exists for Alzheimer's disease. Recent studies have shown that many vascular risk factors and unfavourable lifestyle factors are shared predictors of stroke and dementia,[4] and incident cerebrovascular diseases may precipitate a decline in cognitive function or dementia.[5 6] This suggests that some cognitive impairment and dementia might be prevented by preventing cerebrovascular diseases.[7]

Cognitive impairment in cerebrovascular diseases

Cerebrovascular diseases include a variety of medical conditions that affect the blood vessels of the brain and the cerebral circulation. These include conditions that may cause acute interruption of cerebral circulation and subsequent acute neuronal damage, such as ischaemic or haemorrhagic stroke, and disorders that may cause chronic pathological changes in small vessels and neurological dysfunction, such as cerebral small vessel diseases. Patients with cerebrovascular diseases, both acute and chronic, usually have multidimensional functional impairments to the brain and an increased risk of cognitive impairment and dementia.

Globally, approximately one in four adults will develop stroke in their lifetime from the age of 25 years onwards.[8] Functional impairments to the brain due to stroke vary, but physical disability, aphasia, and dysphagia are common and have received the most attention from stroke specialists to date. However, many patients who survive stroke go on to experience cognitive decline, including vascular cognitive impairment and other dementias, and these aspects have received less attention from either stroke specialists or dementia specialists. This is unfortunate, as incident stroke is associated with an acute decline in cognitive function, especially in global cognition and executive function.[5] The incidence of post-event dementia at one year in patients with the mildest stroke symptoms (that is, transient ischaemic attack and minor stroke) ranges from 5-8% to 19% but may reach more than 34% in those with severe stroke, nearly 50 times higher than in the general population.[6 9] Cognitive decline also accelerates and persists over many years,[5] and it could be as high as 44% at three years after a minor stroke and be the main factor preventing independence or return to work.[9]

Another form of cerebrovascular disease that has received less attention from neurological specialists is chronic damage to the small vessels in the brain. The features of cerebral small vessel diseases seen on brain imaging include lacunas, white matter hyperintensity, and cerebral microbleeds, as well as various other features. A population based study showed that more than 70% of people aged 50 years or older presented with at least one kind of cerebral small vessel disease.[10] Cerebral small vessel disease is not fully understood, but it is associated with chronic damage to small vessels that may lead to blockage or leakage of small vessels in the brain.[11] As the chronic damage accumulates, patients with cerebral small vessel disease can present with acute stroke syndromes, mild cognitive impairment or dementia, gait and balance problems, mood disorders, and urinary incontinence, depending on the location of the lesions.[11] Cerebral small vessel disease is one of the most common causes of vascular dementia and is also frequently found alongside Alzheimer's disease pathology.[7 11] Cerebral small vessel disease is estimated to contribute 45-50% of all cases of dementia.[11]

The cognitive consequences of cerebrovascular disease may substantially affect patients' quality of life and cause a considerable disease burden for patients and their families.[9] Compared with other brain dysfunctions such as movement disorders, cognitive impairment and dementia due to cerebrovascular diseases are neglected by both patients and physicians in all countries, but especially in low income and developing countries such as China.

Mechanisms of cognitive impairment in cerebrovascular diseases

Given the high prevalence of cognitive impairment, understanding the mechanisms of cognitive impairment in cerebrovascular diseases is pivotal. Understanding impairment of brain function due to neuronal damage after stroke is not difficult. A recent study suggested that multiple infarcts in one hemisphere; involvement of strategic regions such as the middle and inferior frontal gyri, parietal region, and middle temporal gyrus; larger stroke lesion volume; and lesions on the left hemisphere were associated with a higher risk

KEY MESSAGES

- Patients with cerebrovascular diseases, including both stroke and small vessel disease, have an increased risk of cognitive impairment and dementia
- Vascular factors contribute to the pathophysiological progress of cognitive impairment and dementia, which offers a new dawn of preventing dementia by preventing cerebrovascular diseases
- Further studies are needed to understand the mechanisms of cognitive impairment and explore effective approaches to prevent dementia by preventing cerebrovascular diseases

of dementia after stroke.[12] Further studies are needed in large populations to confirm these findings and enable application of a personalised approach in the clinic.

Despite cognitive impairment after cerebral small vessel disease being a common cause of impairment of brain function, its underlying pathogenesis and mechanism are poorly understood. Recent studies showed that early impairment of cognition may be induced by disruption of the glio-neuro-vascular unit.[7 13] Small vessel pathologies due to vascular risk factors may induce breakdown in the integrity of the blood-brain barrier and cerebral blood flow deficits.[7 13] Although not yet tested in prospective longitudinal studies, structural and functional alterations of cerebral small vessels may trigger the cascade of molecular signals (for example, activation of innate immunity, vascular oxidative stress, and inflammation), leading to disruption of the glio-neuro-vascular unit.[7] Neurovascular dysfunction alters the homeostasis of the brain microenvironment and promotes accumulation of amyloid and tau protein in regions involved in cognition, leading to early vascular and neurodegenerative cognitive impairment.[7] Accumulation of amyloid and tau protein in cerebrospinal fluid and changes in their concentrations in the brain may contribute to pathophysiological progression from no cognitive impairment to mild cognitive impairment to Alzheimer's disease.

Recent progress in imaging techniques has provided potential breakthroughs in our understanding of the mechanism of cognitive impairment. Clinical studies have shown endothelial dysfunction in cerebral microvessels in cerebral small vessel disease, including blood-brain barrier dysfunction, dysfunctional blood flow, impaired interstitial fluid drainage, and white matter rarefaction.[11] However, challenges still exist to determine what types of vascular dysfunction initiate or propagate small vessel disease pathogenesis, which abnormalities are reversible, and why lesion progression and symptomatology are so variable (box 1).[11] Clarification of these questions may facilitate identification of potential therapeutic targets to improve brain function after cerebrovascular diseases.[14]

Preventing dementia by preventing cerebrovascular diseases

Screening for cognitive impairment using scales such as the Montreal Cognitive Assessment (MoCA) is easy. However, although the US Food and Drug Administration recently accepted an application for the first biological treatment (aducanumab) of Alzheimer's disease, treatment of the disease is still disappointing owing to the failure of most recent trials targeting clearance of amyloid and selective inhibition of tau protein aggregation to improve cognition in Alzheimer's disease.[15 16] Increasing evidence points to a failure of clearance of amyloid and tau rather than overproduction as a main problem in Alzheimer's disease, and this failure is related to hypertension and other vascular risk factors through functional alteration of perivascular space clearance, implicating new directions to prevent dementia by preventing cerebrovascular diseases.[17] This may help to identify new therapeutic targets to prevent cognitive impairment, including protection of the glio-neuro-vascular unit (box 1).[14]

Cerebrovascular diseases and dementia share some, largely modifiable, risk factors and protective factors.[4] Growing clinical evidence shows that vascular risk factors contribute to cognitive impairment. General cardiovascular risk was shown to be associated with longitudinal cognitive decline in clinically normal older adults, both alone and synergistically with β-amyloid burden.[18] Adherence to the Life's Simple 7 advice for ideal cardiovascular health (stop smoking, eat better, lose weight, control cholesterol, get active, reduce blood sugar, and manage blood pressure) in midlife was associated with a lower risk of dementia later in life in the Whitehall II cohort study and was recommended by the American Heart Association/American Stroke Association Presidential Advisory to maintain optimal brain health.[19 20] The Lancet Commission on Dementia Prevention, Intervention, and Care proposed a life course model of dementia risk that reflects how lifestyle factors across the lifespan contribute to risk of dementia. They estimated that 12 modifiable lifestyle factors across the lifespan accounted for approximately 40% of worldwide dementias, among which vascular risk factors (midlife hypertension, alcohol misuse, and obesity; later life smoking, physical inactivity, and diabetes) accounted for approximately 11%.[21] A recent study showed that vascular risk factors (diabetes, midlife hypertension, midlife obesity, physical inactivity, and smoking) accounted for approximately 21% of Alzheimer's disease and 17% of vascular dementia.[22] Assuming a 20% reduction in the prevalence of above vascular risk factors, depression, and low educational level implied a 6.4% and 6.5% reduction in the prevalence of Alzheimer's disease and vascular dementia.[22] Considering that approximately 90% of stroke is attributable to modifiable risk factors,[23] preventing dementia by controlling vascular risk factors and cerebrovascular diseases may be promising. Nevertheless, a systematic review conducted by the Agency for Healthcare Research and Quality concluded that insufficient high strength evidence existed to justify a public health campaign to encourage people to adopt lifestyle interventions to prevent or slow cognitive decline and dementia.[24]

Box 1: Advances in research on preventing dementia by preventing cerebrovascular diseases

Where we are
- Early impairment of cognition may be induced by disruption of the glio-neuro-vascular unit
- Neurovascular dysfunction may promote both early vascular and neurodegenerative cognitive impairment
- Vascular risk factors, such as diabetes, midlife hypertension, midlife obesity, physical inactivity, and smoking, are associated with both vascular dementia and Alzheimer's disease
- Insufficient high strength evidence exists for lifestyle interventions to prevent or slow cognitive decline and for drugs to improve cognitive impairment after cerebrovascular disease

What the prospects are
- In-depth research is needed on the types of vascular dysfunction that initiate or propagate small vessel disease pathogenesis, which abnormalities are reversible, and why lesion progression and symptomatology are so variable
- Ways need to be found to prevent dementia by improving management of vascular risk factors and testing drugs that may improve the glio-neuro-vascular unit

As cerebrovascular diseases and dementia are so closely interlinked, amelioration of vascular risk and vascular damage offers a new dawn for preventing not only vascular dementia but also mixed and even Alzheimer's dementias, and it may even offer alternative routes to clear amyloid and tau protein aggregation. Neurons are not renewable, and impairment of brain function is often irreversible. Therefore, very few effective approaches are available for patients with cerebrovascular diseases and cognitive impairment, although scope for repurposing exists. For example, one study suggested that nimodipine might reduce memory impairment after acute ischaemic stroke.[25] Similarly, drugs with endothelial and glial protection and anti-inflammatory properties, such as cilostazol, are being trialled to prevent and treat cerebral small vessel diseases and reduce cognitive impairment (for example, http://www.isrctn.com/ISRCTN14911850). As cerebral small vessel disease is associated with vascular risk factors, particularly hypertension, intensive control of vascular risk factors such as hypertension has been evaluated, although with mixed results.[14] For example, a substudy of the SPRINT MIND (Systolic Blood Pressure Intervention Trial Memory and Cognition in Decreased Hypertension) trial showed that intensive blood pressure reduction decreased progression of white matter hyperintensities, mild cognitive impairment, and probable dementia.[26] The results of these trials indicated that patients with cerebrovascular disease or vascular risk factors might be a potential target population to prevent dementia. As cerebrovascular disease and vascular risk factors are so common, these converging epidemiological and clinical trial results justify further efforts to find ways to prevent dementia by improving management of vascular risk factors and testing drugs that may improve the function of the endothelium and other parts of the glio-neuro-vascular unit.

In summary, patients with cerebrovascular diseases have a substantial risk of cognitive impairment. Vascular factors contribute to the pathophysiological progress of cognitive impairment, providing new opportunities for preventing not only vascular dementia but also mixed and potentially even Alzheimer's dementias by testing prevention strategies that work for cerebrovascular diseases. Further studies are needed to understand the mechanism by which cerebrovascular disease accelerates Alzheimer's, mixed, and vascular dementias and to test interventions targeting vascular risk factors and people with cerebrovascular diseases to prevent dementia.

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