What existing drugs classes could be relevant for disease-modifying strategy in vascular cognitive impairment and vascular dementia?

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Cognitive dysfunction frequently occurs following stroke and is an important cause of stroke-related morbidity. The growing health, social and economic burden of post-stroke cognitive impairment (PSCI) is driving the demand for clinical studies that evaluate the benefits and risks of pharmacological and nonpharmacological therapies.

There is a huge variability in terms of manifestation of cognitive decline after a stroke; however, often there is a delay, that could provide unique opportunities for disease modifying strategies to be applied to preserve cognition following stroke.

Prevention and treatment of PSCI are the critical priorities for clinical care and research. Better understanding of the risk factors and estimation of the risk scores for post-stroke dementia are important for selection of patients for preventive clinical trials.

Studies on mechanisms and predictors of post stroke dementia could provide the keys for preventive and disease-modifying treatment. DEDEMAS (Determinants of Dementia After Stroke) study is looking on biological markers (neuroimaging, biochemical markers derived from blood) and on interactions between vascular and neurodegenerative mechanisms. The Tel-Aviv Brain Acute Stroke Cohort (TABASCO) trial, with up to 10 years’ follow-up after stroke, is focused on the association between predefined demographic, psychological, inflammatory, biochemical, neuroimaging and genetic markers, measured during the acute phase.

The treatment of vascular risk factors offers possibilities for prevention and probably for impact on progression of the disease. Obesity, metabolic syndrome, physical inactivity, hypertension, hypercholesterolaemia and others are associated with cognitive decline and dementia.

The association of diabetes, stroke and dementia is well-known. Compared with the general population, people with type 2 diabetes have a 1.5–2.5 times increased risk of dementia, and at present one in ten to 15 cases of dementia can be attributed to type 2 diabetes. At the cellular level, type 2 diabetes is associated with mitochondrial dysfunction, endoplasmic reticulum stress, increased inflammation, and altered energy metabolism. Antidiabetic drugs improve hyperglycaemia, dyslipidaemia, insulin resistance, and can counteract tissue inflammation associated with type 2 diabetes. A number of antidiabetic drugs, like metformin, thiazolidinediones, and compounds targeting the glucagon-like peptide-1 receptor affect brain metabolism, neuroinflammation, and regeneration. These antidiabetic drugs could be developed as disease-modifying therapies for human brain diseases in patients with and without diabetes.
There are several important avenues in the vascular dementia treatment: symptomatic improvement of the core symptoms (cognition, function, and behavior), slowing of progression, treatment of neuropsychiatric symptoms.

In vascular dementias, with their multifactorial pathogenesis, there is a need to consider drug combinations or multimodal agents to change the course of the disease.

One of the promising strategies of the modifying therapies has been associated with the use of neurotrophic factors. There is an increasing evidence that alterations in the brain neurotrophic support and in particular BDNF and NGF expression and signaling might contribute to neurodegeneration. Cerebrolysin is a peptide preparation with neurotrophic activity demonstrated in various models in vitro and in vivo; its mechanism of action might involve modulation of the pro-NGF/NGF balance and a concomitant protection of cholinergic neurons. The results of the large, multicenter, double-blind, placebo-controlled study in VaD demonstrated that the drug significantly improved the clinical outcome in VaD patients; it was safe and well tolerated. The Cochrane review stated that cerebrolysin may have positive effects on cognitive function and global function in elderly patients with vascular dementia of mild to moderate severity.

Actovegin, a deproteinized ultrafiltrate of calf blood comprising more than 200 bioactive constituents exhibits a range of pleiotropic neuroprotective and metabolic effects. A study in a rat model of transient global cerebral ischaemia found that it improved spatial learning and memory. The recently competed ARTEMIDA study showed that actovegin (2000mg i.v. solution for up to 20 daily infusions followed by 1200 mg/day orally for the remainder of the 6 month period) improved cognitive outcomes in patients with PSCI, compared with placebo.

ACE-inhibitors and memantine are currently widely used in vascular dementia. Controlled clinical trials with donepezil and galantamine demonstrated improvement in cognition, behaviour and activities of daily living. Trials using memantine showed that it was well tolerated, improved function and reduced care dependency in treated patients compared with placebo.

Evidence-based assessment of the efficacy and safety of the number of interventions including antidepressants and hyperbaric oxygen therapy have been published.

Some other strategies look promising, also in terms of the disease-modification. A better understanding of the cellular and molecular processes involved in neurovascular unit dysfunction may lead to improved treatments for PSCI.

An increasing attention is being paid to anti-inflammatory strategies, as recent studies suggested that the extension and persistence of neuroinflammation after stroke may interact with pre-existing AD pathology and accelerate neurodegeneration.

More translational studies are needed to better understand the molecular mechanisms contributing to neuronal damage in PSCI. Properly designed interventions with
multifactorial effects are needed to establish disease-modifying therapy and to improve prognosis of patients with cognitive impairment after stroke.

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