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Review

Clinical Effect of Carotid Stenting on Cognitive Abilities – Possible Evaluation Using Candidates for Biomarkers

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Abstract

Micro- and macrovascular consequences of atherosclerosis, arterial hypertension, dyslipidemia, and smoking can affect neurotransmission and markers for neuronal activity. The potential direction and specifics are under study. It is also known that optimal control of hypertension, diabetes, and dyslipidemia in midlife may positively affect cognitive functioning later in life. However, the role of hemodynamically significant carotid stenoses in neuronal activity markers and cognitive functioning is still being debated. With the increased use of interventional treatment for extracranial carotid disease, the question of whether it might affect neuronal activity indicators and whether we can stop or even reverse the path of cognitive deterioration in patients with hemodynamically severe carotid stenoses naturally emerges. The existing state of knowledge provides us with ambiguous answers. We sought the literature for possible markers of neuronal activity that can explain any potential difference in cognitive outcomes and guide us in the assessment of patients throughout carotid stenting. The combination of biochemical markers for neuronal activity with neuropsychological assessment and neuroimaging may be important from practical point of view and may provide the answer to the question for the consequences of carotid stenting for long-term cognitive prognosis.

Keywords

BDNF, carotid stenting, cognitive impairment, dementia, FABP7, NGF, VEGF, neurotrophins, neurofilament light, S100 protein

INTRODUCTION

There are three major types of candidate biomarkers that may potentially be responsive to cerebral hemodynamics, can be followed, and assessed at the time of carotid stenting: 1. biomarkers of neuronal activity and repair (neurotrophins); 2. structural neuronal molecules, and 3. endothelium derived molecules with the function of neurotransmitters.

The development and the survival of the neurons are at least partly dependent on extracellular regulation from the neurotrophins. These molecules have a major role in the proliferation, migration, and the phenotypic differentia-

tion of the neural cells. They ensure neural structural and functional integrity. Several proteins are included in this group, among them the neuronal growth factor (NGF), the brain-derived neurotrophic factor (BDNF), the neurotrophin-3 (NT-3), neurotrophin-4/5 (NT-4/5), all of which have 50% coincidence in their amino acid sequence, and neurofilament light chain.[1] Some significance may also have the neurotransmitters and structural proteins, such as the neuron specific enolase (NSE), S100B, or endothelium derived molecules such as vascular endothelial growth factor (VEGF).

The regulation, serum concentration, and functional modulation of biomarkers for neuronal activity in patients with extra- and intracranial atherosclerotic disease are an evolving field, especially in terms of invasive interventional treatment. It would be of significant value if we could define a set of biomarkers that would have a prognostic implication for mid- and long-term interventional outcomes.

The aim of this review is to discuss several promising biochemical markers for neuronal activity, which may prove of prognostic value in clinical practice. Another aspect of the problem is how to properly and easily assess clinical effectiveness and neuronal functioning in real practice. One possible way is directly with neuroimaging – computer tomography, functional magnetic resonance, near infrared optical tomography. This will be discussed elsewhere. Another possible way is indirectly with the assessment of cognition via neuropsychological tests as a surrogate marker. In the current review, we tried to correlate biochemical biomarkers with neuropsychological outcome in patients with extracranial carotid stenosis-revascularization.

CANDIDATE BIOMARKERS

Brain derived neurotrophic factor (BDNF)

BDNF has a very important role for the function of many neuronal groups in the dorsal ganglia[2] and in the cortical and hippocampal neurons.[3] Furthermore, BDNF reduces the inhibitory effect GABA on transmission by modulating the phosphorylation of GABAa receptors.[4] BDNF stimulates the neurogenesis by activation of TrkB and then MAP kinase and PI-3 kinase pathways.[5] This protein is important for the memory processes. Mutations in 5‘ pro-region in people are associated with worse episodic memory than normal.[6] It has been proven that it plays a role in the pain transduction. Its inhibition leads to damping of the central susceptibility of pain.[7] One of the major roles of BDNF for the clinical practice is involvement in the pathogenesis of the neurodegenerative diseases. This is the basis for the search of its future application as a therapeutic agent as well as its use to monitor the effect of treatment. In neurologic diseases, its expression is reduced. [8] There is a selective reduction in the mRNA of BDNF in the hippocampus in Alzheimer's disease patients, and in the substance nigra in Parkinson's disease patients.[9] BDNF was discovered in 1982 and up to the present time, its major role has been associated with memory and neuronal plasticity. In recent years, few scientific papers have correlated the plasma levels of BDNF with dementia or diabetes mellitus.[10] Lasek-Bal[11] found that low plasma concentrations of BDNF at the time of stroke and the early post-stroke period were a marker for poor functional outcome on intermediate follow-up. The main pathogenetic mechanism behind the poor outcome was the role of BDNF in the reversal of the negative effects of ischemia and the impaired structural remodeling, as well as reduced potentiation of synapses. Animal studies[12] have demonstrated that high BDNF levels are associated with reduction of the infarcted area in stroke. The data for its significance in patients with carotid disease is scarce. On the other hand, BDNF can be viewed as a marker of endothelial dysfunction[13] as well, which may be encountered in atherosclerotic carotid disease. Amadio et al.[14] found a correlation between BDNF serum concentration and coronary plaque morphology. However, there is no information for carotid atherosclerotic disease in this aspect.

To conclude, with reference to BDNF as a potential marker for functional outcome in stenting of the extracranial carotid segment, it can be associated both with endothelia functioning and hemodynamic stress, as well as with neuronal functioning. These processes, however, are also physiologically associated and their artificial separation for scientific purposes may be impossible.

Neuronal growth factor (NGF)

NGF participates in the growth and differentiation of the sympathetic and some sensory neurons.[15] It is of major significance for the functional integrity of the cholinergic neurons in the central neural system.[16] It is produced by every peripheral tissue that is innervated from sensory afferent and/or sympathetic efferent pathways, the central and peripheral neural system, and some immune cells. Its cytosolic activity is maintained via TrhA and *MAP* kinase.[17] In some studies, the down regulation of NGF could be a marker for Alzheimer's disease[18], while the endogenous NGF had nerve repair functions.[19] There are several studies with exogenous NGF directly injected in the cerebrospinal fluid with the aim to treat neurodegenerative disorders[20], to reduce the hypoxic-ischemic brain injury in the neonatal period[20], or for treatment of peripheral neuropathies.[21]

In a rat study[22], the ischemic brain injury in significant atherosclerotic disease was reduced by pseudolentivirus-mediated delivery of beta-NGF into the brain. The result was reduced neuronal apoptosis, increased cell proliferation, reduced cognitive functional impairment via upregulation of GAP-43, which is correlated with hippocampal synaptic plasticity.[23]

The above mentioned studies make it clear that NGF may be a good candidate surrogate marker for cognitive functioning; however, its significance in terms of symptomatic extracranial carotid disease is unknown.[24] NGF

potentiates cardio-vascular system development by paracrine mechanism, blood vessels branching and differentiation.[25] From a practical point of view, vascular scaffolds containing NGF were studied with reference to the ability to enhance re-endothelialization and vascular healing.[26] But it is still not known how the extracranial atherosclerotic plaques affect NGF endothelial secretion, what the consequence is and what can be expected after stenting.

Neurotrophin-3

Genetic studies have demonstrated that NT-3 polymorphism rs6332 had a significant association with executive functioning and for the progression of Alzheimer's disease.[27] In rat studies, due to the intracranial injection of NT-3 after stroke or its application as a gene therapy before stroke, the volume of the ischemic region was significantly reduced[28] and the repair of the locomotor neurons was enhanced by stimulation of the spindle rooting by the neurotrophin[29], NT-3 accelerates endothelial progenitor cells recruitment, endothelial healing and re-endothelialization of injured carotid arteries.[30] Thus NT-3 may have a positive effect in carotid stenting both through a local endothelial healing effect and through paracrine neurohormonal stimulation with direct positive effect on cognition. However, many studies are required to prove and incorporate in clinical practice this hypothesis.

Neurotrophin-4/5

Neurotrophin-4/5 is another member of the neurotrophin family. Its role in ischemic brain injury is not known. There are several reports for a potential correlation in rodents, but such is lacking for humans. In a study, the intraventricular application of NT-4/5 in acute stroke reduced the infarct size.[31]

Vascular endothelial growth factor (VEGF)

VEGF is a cytokine, a member of a large group of proteins that stimulate angiogenesis.[32] Their role after ischemic stroke was proven to be beneficial to the stimulation of the collateralization and consequently perfusion of the ischemic brain tissue. VEGF-A is the main mediator of the brain angiogenesis. Early after stroke, the ischemic neurons stimulate paracrinely the surrounding astrocytes. They disrupt the endothelial barrier through elevated production of endogenous VEGF.[33] VEGF-A dissociates intercellular junctions and enhances the permeability of the blood – brain barrier, which leads to brain edema and poorer functional prognosis.[34] High VEGF levels after stroke are maintained for up to 3 months, and the functional impairment depends on the specific stroke type.[35] Namely, in patients with embolic incidents, the high VEGF levels were associated with significantly poorer neurological outcome, while in atherothrombotic incidents, the correlation was negative. The suppression of VEGF secretion and receptor in rats led to reduction in the ischemic volume.[36] These diverse results come to show, that the functional significance of VEGF in ischemic preconditioning and injury is complicated and depends on the duration, volume, and collateralization.

Another point to be considered in the role of the neuro and angiotrophic factors at the time of central nervous system ischemia is the time of their maximal concentration. [37] The blockage of VEGF in rats reduced brain edema and neuronal death in acute ischemia.[35] However, what is its significance in chronic cerebral hypoperfusion as with significant carotid stenoses with poor collateralization, or in reperfusion after carotid stenting, is not known and there is no information published for the moment.

S100 protein and neuron specific enolase NSE

S100 is a Ca^{2+}-binding protein which, depending on its concentration, can have local trophic or toxic effect.[38] In low concentrations, it stimulates neuronal growth and repair after injury and thus it has neuroprotective effect.[39] NSE is a hydrolytic enzyme synthesized in the neurons – an isoenzyme of the enolase, which catalyzes the transformation of 2-phosphoglycerate in phosphoenolpyruvate. It is secreted in a variety of neuroectodermal tissues and is secreted at the time of ischemia or central nervous system trauma, at which time their concentration in the cerebrospinal fluid rises.[40] Whether they have a potential role in significant carotid stenoses is still under debate and little known.

Neurofilament light chain (NFL)

NFL is a marker for neurodegenerative diseases. It is a component of the large, myelinated axons and its cerebrospinal or plasma levels are elevated in neurodegenerative diseases as amyotrophic lateral sclerosis and Alzheimer's disease.[41] A study of 25 patients with carotid endarterectomy[42] showed that only proinflammatory markers were changed significantly after the carotid intervention, but not the structural markers, one of which was NFL.

Brain fatty lipid-binding protein (FABP7)

FABP7 is important in early astrocyte and neuronal development. Its concentration also shoes diurnal variation, and it was shown that FABP7 was elevated in dementia-related diseases.[43] What its role is in chronic ischemia or reperfusion is still unknown. It can have a potential role in the study of cognitive results after carotid interventions.

Possible correlation of carotid stenoses, biochemical markers for neuronal activity and integrity and neurocognitive tests

Mathiesen et al.[44] showed that patients with asymptomatic (in this study, without stroke or transitory ischemic attack) carotid stenoses had lower results from cognitive testing in comparison with patients without stenoses. The authors concluded that carotid atherosclerosis may have a significant role in the cognitive decline of the individual. In another study of 4006 patients, the asymptomatic carotid disease[45] was associated with cognitive impairment and

damage in the frontal lobe, which is primarily involved in executive functioning. Here comes the question whether "asymptomatic" carotid disease is really asymptomatic or we need to redefine the term by using better criteria: biochemical, neuroimaging and neuropsychological. Potential mechanisms for brain injury in atherosclerotic carotid disease are chronic brain hypoperfusion, silent infarct, white matter lesions, arterial hypertension, arterial stiffness, hypertension, or diabetes induced small-vessel disease. Bearing in mind these contributors to brain injury, a potential confounding factor could be defined, namely, the functional significance of a given atherosclerotic intra and extracranial stenosis. In a study on 208 patients, Cheng et al.[46] showed that there was significant improvement in the executive functioning after carotid stenting They explained the results with the improved cerebral perfusion after the procedure. Other authors failed to show such a positive effect in chronic hypoperfused brain tissue, and found reperfusion defects and decreased executive functioning, which was explained with hemodynamic and oxidative stress.[47] It can be concluded that there are other factors, still unknown to us, which define the success of carotid interventions in terms of executive functioning.

Possible contradictions in carotid interventions in terms of neurotrophic biomarkers

The usefulness of carotid stenting, especially in the acute setting of stroke, is a relatively new and quickly evolving subject. The search for a way to improve the functional capacity after ischemic brain injury (acute and chronic) is gaining speed and the scientific community is on the search of biomarkers that may help to better define the prognosis for patients, as well as to stratify the expected functional (motor and cognitive) benefit after revascularization. Carotid stenting stimulates blood flow and regeneration, reduces ischemic and ischemic brain injury. However, in some cases it may lead to significant edema and reperfusion injury. Carotid interventions, in particular stenting, lead to local stimulation of inflammatory markers such as IL6. They influence blood flow distally and may be the reason for local changes and even hypoperfusion.[48] Such a proinflammatory state may be the reason for lower BDNF levels and, consequently, for reduced neuroplasticity.

The triple correlation between laboratory neural biomarkers, brain perfusion, and cognition before and after stenting may be important for the midterm clinical prognosis in patients with significant carotid stenoses. Laboratory markers may provide the missing link between restoration of cerebral blood flow and the differential impact[49] on functional outcome in terms of cognition.[50]

CONCLUSION

The reperfusion after carotid revascularization can lead to elevated levels of neurotrophin and better functional outcome. It can potentially increase the risk for edema, local inflammation, which in turn can reduce the neurotrophins. These seemingly conflicting effects may be intimately correlated and the precise outcome in each patient may rely on factors still unknown for the general practice. A difference should be made between neurotrophic factors, inflammatory proteins and growth cytokines, and structural neuronal proteins. These different groups of markers may change independently in chronic ischemia-reperfusion and may have different significance. However, the need for better prognostication, both functional and cognitive, stimulates the search of the precise mechanisms and effects of neurotrophic and vasotrophic factors in chronic brain ischemia and their correlation with the results of carotid interventions.

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Conflicts of Interest

The authors have no conflicts of interest to declare.

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Клиническое влияние стентирования сонных артерий на когнитивные способности – возможная оценка с использованием кандидатов в биомаркеры

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Резюме

Микро- и макрососудистые последствия атеросклероза, артериальной гипертензии, дислипидемии и курения могут влиять на нейротрансмиссию и маркеры активности нейронов. Потенциальное направление и особенности находятся в стадии изучения. Также известно, что оптимальный контроль артериальной гипертензии, диабета и дислипидемии в среднем возрасте может положительно влиять на когнитивные функции в более позднем возрасте. Тем не менее, роль гемодинамически значимых стенозов сонных артерий в маркерах активности нейронов и когнитивных функциях всё ещё обсуждается. С увеличением использования интервенционного лечения экстракраниального каротидного заболевания естественным образом возникает вопрос о том, может ли оно повлиять на показатели активности нейронов и можем ли мы остановить или даже обратить вспять путь когнитивного ухудшения у пациентов с гемодинамически тяжёлым стенозом сонных артерий. Актуальная на настоящий момент информация не предлагает нам однозначных ответов. Мы провели поиск в литературе возможных маркеров активности нейронов, которые могли бы объяснить любую потенциальную разницу в когнитивных результатах и помочь нам в оценке пациентов во время стентирования сонных артерий. Сочетание биохимических маркеров активности нейронов с нейропсихологической оценкой и нейровизуализацией может быть важным с практической точки зрения и может дать ответ на вопрос о последствиях каротидного стентирования для долгосрочного когнитивного прогноза.

Ключевые слова

BDNF, стентирование сонных артерий, когнитивные нарушения, деменция, FABP7, NGF, VEGF, нейротрофины, свет нейрофиламентов, белок S100