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Endothelial dysfunction in stroke

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Abstract

The endothelium consists of one layer of endothelial cells which cover the inner layer of the blood and lymph vessels. The endothelium is involved in the regulation of vascular tone and structure, inflammation and thrombosis by releasing various agonistic and antagonistic molecules to maintain homeostasis. Endothelial dysfunction signifies defects of the endothelial cells. Many published studies strongly support the hypothesis that endothelial dysfunction is an essential component of atherosclerosis and its presence is a risk factor for the development of various clinical events, such as stroke. The search for specific biomarkers of endothelial dysfunction can have important clinical significance. Identification and monitoring of biomarkers of endothelial dysfunction could contribute to stroke diagnosis, prognosis and development of therapeutic strategies.

Keywords: biomarkers; blood-brain barrier; endothelial cells; endothelial dysfunction; stroke

Sažetak:

Endotelna difunkcija u moždanog udara

Endotel je građen od jednog sloja endotelnih stanica, koje oblažu unutarnji sloj krvnih i limfnih žila. Endotel je uključen u regulaciju vaskularnog tonusa, upale i tromboze otpuštanjem različitih agonističkih i antagonističkih molekula koje održavaju homeostazu. Endotelna disfunkcija označava oštećenje endotelnih stanica. Dosadašnje studije podržavaju hipotezu o endotelnoj disfunkciji kao važnoj komponenti razvoja ateroskleroze, također smatra se faktorom rizika za razne kliničke događaje, poput moždanog udara. Istraživanje specifičnih biomarkera endotelne disfunkcije može imati važno kliničko značenje. Identifikacija i praćenje biomarkera endotelne disfunkcije može doprinijeti dijagnosticiranju moždanog udara, prognozi i razvoju terapijskih opcija.

Ključne riječi: biomarkeri; endotelna disfunkcija; endotelne stanice; krvno-moždana barijere; moždani udar

Introduction

The endothelium is a single layer of squamous endothelial cells which cover the inner layer of blood and lymph vessels (1). The endothelium forms an interface between the circulating blood or lymph in the lumen and the rest of the vessel wall. Endothelial cells form a protective barrier between vessels and tissue, control the flow of substances and fluid into and out of a tissue. The endothelium is involved in the regulation of vascular tone and structure, inflammation and thrombosis by releasing various agonistic and antagonistic molecules to maintain homeostasis (2). Endothelial dysfunction has been observed in stroke patients and has been associated to stroke physiopathology, clinical severity and outcomes (3). It is an important step in the atherosclerotic disease process and contributes to enhanced plaque vulnerability, triggers plaque rupture and favours thrombus formation. Many published researches and studies so far strongly support the hypothesis that endothelial dysfunction is an essential component of atherosclerosis and its presence is a risk factor for the development of various clinical events, such as stroke (2,3). Acute ischemic stroke is associated with an increase of endothelial activation markers in the systemic circulation (3). Ischemia is known to impair endothelium-dependent vasodilation, thereby limiting blood flow restoration and inducing a prothrombogenic and proinflammatory endothelial phenotype (4). It is important to understand this complex and damaging neurological condition, as stroke is the leading cause of morbidity and mortality worldwide.

Stroke

Stroke is defined by the World Health Organization as a clinical syndrome consisting of rapidly developing clinical signs of focal (or global in case of coma) disturbance of cerebral function lasting more than 24 hours or leading to death with no apparent cause other than a vascular origin (5).

According to the World Stroke Organization, over 13.7 million incidents of stroke are reported every year, with 60% being in patients under the age of 70. In Europe, stroke is the second most common cause of death after ischemic heart disease, accounting for around 1 million deaths per year. The lifetime risk of stroke is approximately one in four up to the age of 80 (6). The incidence of stroke increases with age and doubles after the age of 55. The incidence of stroke varies between men and women based on age. It is higher in younger aged women, whereas incidence increases slightly with older age in men. The higher risk for stroke in women is due to factors related to pregnancy, such as preeclampsia, use of hormonal contraception or other hormonal therapy. Age-specific mortality rates increase with age and are higher in men than in women for all age groups, except at the age of 80+ when the mortality rates in women are higher than in men (7).

A stroke can present with a number of different symptoms, including facial numbness and weakness, visual impairment, weakness of upper or lower limbs on one side of the body, impaired balance, nausea, dizziness, abrupt severe headache and speech impairment. These traditional symptoms are reported to present equally in men and women, but women are more likely to present with more atypical symptoms of acute stroke compared with men, which may lead to delayed diagnosis. These atypical symptoms may include altered consciousness or mental status, fatigue, drowsiness, incontinence, facial and limb pain, and general weakness. Women also experience nausea, chest pain, shortness of breath, palpitations, and hiccups. Patients often suffer from neurologic sequelae as well as increased likelihood of hospital readmission and complications such as infections, venous thromboembolism, falls and fractures (7,8). The acronym FAST was developed to easily and quickly recognize the symptoms of stroke in the general population. FAST stands for facial droop, arm weakness, slurred speech and time of onset. It is a very simple and fast tool which helps us recognize signs of stroke as early as possible and consequently to diagnose and treat it in a timely manner (8).

Stroke can be broadly classified into ischemic stroke and hemorrhagic stroke, the latter of which includes intracerebral haemorrhage (ICH) and subarachnoid hemorrhage depending on the site of blood spillage. Hemorrhagic strokes are caused by rupture of a blood vessel inside the brain and ischemic strokes are caused by blockage of an artery in the brain. Both conditions cause local hypoxia which damages brain tissue.

Acute ischemic stroke (AIS) is the most common, accounting for approximately 85% of cases (9). There are several pathophysiological mechanisms underlying AIS. Thromboembolism, cardioembolism, small vessel disease and cryptogenic are frequently observed mechanisms. Other less common mechanisms include arterial dissection, vasculitis, vasculopathy and hematological disorders such as hypercoagulable states and sickle cell disease. Most ischemic strokes are thromboembolic in origin, with common sources of embolism being large artery atherosclerosis and cardiac diseases, particularly atrial fibrillation. Fast and accurate diagnosis of stroke is critical for choosing the appropriate acute stroke treatment, such as intravenous tissue plasminogen activator (IV tPA) or endovascular mechanical thrombectomy (10). The relevance of acute ischemic stroke detection is emphasized by the term “time is brain”. The primary therapeutic goal in the treatment of acute stroke is the timely restoration of blood flow to the salvageable ischemic brain tissue at risk for cerebral infarction. Recanalization and reperfusion of the occluded vessel have been shown to reduce the infarct size and reverse neurological deficits (11).

In the long term, treatment aims to reduce the likelihood of another stroke, known as secondary prevention. Options for secondary prevention of ischemic stroke include antiplatelet and

anticoagulant therapy, statins, antihypertensive therapy and antidiabetic agents among others. In addition, some lifestyle changes are also necessary, such as a healthy diet, regular exercise, quitting smoking and limiting alcohol consumption (12).

Risk Factors

Risk factors for stroke can be divided into two categories: modifiable and non-modifiable. Age, sex, race and genetics are non-modifiable risk factors while hypertension, atrial fibrillation, cigarette smoking, diet and physical inactivity are commonly reported as modifiable risk factors. Triggers for stroke also include inflammatory disorders, infections, pollution and other cardiac disorders (13). The incidence of stroke increases with age, doubling after the age of 55, for both men and women (13,14). Several studies have shown that race/ethnicity is related to stroke incidence and mortality. Hispanics and blacks have a higher risk for stroke and increased mortality rates. Blacks are more than twice as likely to die of stroke compared to whites, especially in younger age groups (14).

Genetic factors can also contribute to stroke risk. Epidemiology studies showed that family history of stroke increases the risk by 30% (15). Some rare single gene disorders can contribute to syndromes where stroke is the manifestation, for example, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy is associated with mutations of the Notch3 gene, located on chromosome 19q12 (16). In addition, single gene disorders can also cause syndromes where stroke is just one of symptoms, for example, sickle cell anemia. Although genetic factors are considered non-modifiable, genetic therapy may change this in the future.

Hypertension is most important modifiable risk factor. Studies have shown an increased risk of stroke associated with all degrees of hypertension, isolated systolic hypertension and diastolic blood pressure (17). The risk for stroke increases with the elevation in blood pressure. Treatment trials demonstrated a benefit of antihypertensive therapy in reducing the incidence of stroke and overall mortality.

Atrial fibrillation has been recognized as a major risk factor for stroke. One study has shown that stroke related to atrial fibrillation has tripled in the last three decades (18). Other studies show that the risk of stroke is 17 times higher among those with chronic atrial fibrillation associated with valvular heart disease and 5 times higher among those with atrial fibrillation without valvular disease (14,18). In addition, atrial fibrillation can be responsible for 25% of strokes in elderly between 80-89 years of age. Other heart diseases such as recent myocardial infarction, significant left ventricular dysfunction with mural thrombus, valvular heart disease, patent foramen ovale, mitral valve strands, aortic arch atheroma and left ventricular hypertrophy are recognized as risk factors as well.

Stroke is the cause of approximately 20% of deaths in patients with diabetes. Stroke risk is also increased by the duration od diabetes, especially for those with diabetes mellitus for ≥10 years. Patients with diabetes who suffered from stroke are likely to be younger and have additional stroke risks.

Increased risk for ischemic stroke is associated with increased total cholesterol, while it decreases in association to elevated high-density lipoprotein cholesterol (19,20).

Cigarette smoking remains one of important stroke risk factors. Studies suggest that those who smoked more than two packs daily were twice as likely to suffer from stroke compared to those who smoked less than 10 cigarettes daily and it is reported that smoking contributes to approximately 15% stroke deaths per year (21).

Diet reduces the risk of stroke but also helps control other risk factors including hypertension, diabetes and dyslipidemia. Physical inactivity, combined with obesity, increases the risk of stroke. Engaging in at least 30 minutes of physical activity daily reduces the risk of premature death from cardiovascular and cerebrovascular diseases.

Endothelial Dysfunction

The endothelium consists of one layer of endothelial cells which cover the inner layer of the blood vessels and lymphatic system. It is in direct contact with blood and lymph. It shows a wide range of phenotypic heterogeneity depending on different needs. The function of these cells varies between organs. In the brain they have an important role in forming the blood-brain barrier. Historically, it was considered as only a barrier protecting the vessel wall, but today it is known that endotelium has a higher significance. Endothelium produces a wide range of factors which regulate vascular tone, platelete aggregation and inflammation (22,23,24). Endothelial cells are metabolically active and their functions are regulated by releasing various substances and enzymes.

Cerebral endothelium forms the blood-brain barrier and it is the first barrier between the brain and systemic circulation. The brain accounts to approximately one forth of total body oxygen usage, therefore making it sensitive to oxidative stress. Endothelial cells maintain vascular tone by regulating production of vasodilators and vasoconstrictors (25). Vasodilators are nitric oxide and prostacyclin, whereas vasoconstrictors are endothelin-1 and angiotensin II. Prostacyclin also has antithrombotic properties. Nitric oxide relaxes smooth muscle cells and prevents leukocyte migaration into the arterial wall. Endothelial cells also prevent aggregation and activation of platelets, but when the endothelium is disrupted circulating platelets adhere to subendothelial structures and coagulation is initiated. Endothelial cells are included in regulation of hemostasis. Hemostasis is regulated with Von Willebrand factor which promotes platelet aggregation (26).

Endothelial dysfunction signifies defects of the endothelial cells which contributes to atherotrombosis, arterial and venous thrombosis. In addition, known cardiovascular risk factors like smoking, aging, diabetes and hypertension contribute to endothelial dysfunction, leading to impaired vasodilatation, increased oxidative stress and inflammatory response which can lead to ischemic stroke and cerebral small vessel diseases. This occurs when bioavailability of nitric oxide is limited. Changes to the vascular structure leads to disruption of the blood-brain barrier and migration of leukocytes from blood into the brain and therefore neuroinflamation starts.

Cerebral ischemia can cause endothelial dysfunction and therefore contribute to more parenchymal damage. It is important to know that stroke is the leading cause of disability worldwide. The role of endothelial dysfunction in stroke is critical (27).

Not all strokes are of known origin and are therefore called cryptogenic. They are more common in younger patients. Some studies showed that younger patients have a higher rate of reccurence after transiet ischemic attack or after ischemic stroke (28). Endothelial disfunction might be one of the mechanisms inducing cryptogenic strokes and we need further studies to confirm or deny this. Endothelial damage is subtle and progressive. It affects cerebral blood flow, leading to prothrombotic state and disruption of the blood-brain barrier and subsequent hypoxic state. Studies have shown that endothelial dysfunction precedes the development of atherosclerosis. Endothelial function can be improved by statins and ACE inhibitors (29).

Vascular pathology is the most common cause of central nervous system dysfunction. As part of this process endothelial cell death occurs making it a potential target for new treatment options.

Biomarkers of Endothelial Dysfunction

Biomarkers are substances that can be measured and used for evaluation and follow up regarding diagnosis, treatments and prognosis. The search for specific biomarkers of endothelial dysfunction can have important clinical significance. It is essential to develop and implement the biomarkers responsible for effective and successful brain recovery (30). Alterations in integrity of the endothelium plays an important role in pathogenesis of stroke. Endothelial dysfunction can be detected by measuring blood markers that are released into circulation after endothelial injury. Some of the biomarkers can be associated with stroke trough endothelial dysfunction, for example enzyme endothelial nitric oxide synthase (eNOS), vascular cell adhesion molecule (VCAM) and intracellular adhesion molecule (ICAM), von Willebrand factor (vWF), endothelial progenitor cells (EPC), interleukin-6 (IL-6).

Endothelial derived nitric oxide (NO) is important for vasodilatation, inhibition of platelet aggregation and supression of inflammatory cells. When endothelial cells are dysfunctional there is a lack of NO production which leads to vasoconstriction, impaired cerebral blood flow and brain ischemia. Decreased synthesis and activation of NO are considered as one of the earliest and most important events which initiate endothelial dysfunction and thrombosis (31). Oxidative stress can produce excessive superoxide, which interacts with NO (32). Enzyme endothelial NO synthase converts L-arginine to NO. Lower levels of this enzyme lead to reduction of NO production.

NO also limits expression of inflammatory mediators such as vascular cell adhesion molecule and intracellular adhesion molecule. In homeostatic state these molecules are expressed at low levels in the brain vasculature and endothelial cells have a limited adhesiveness to leukocytes (33). When there is lack of NO, the inflammatory potential of VCAM-1 and ICAM-1 increases. In addition, these molecules are activated as a response to various cytokines produced during inflammation. The aforementioned leads to leukocyte inflitration and migration trough the endotelium and consequently inflammation. The soluble forms of these molecules are released from cell surface to circulation and can help to quantify endothelial dysfunction (34). It is shown that ICAM-1 is involved in inflammation during reperfusion injury leading to brain parenchyma destruction and hemorrhage.

Endothelial cells produce von Willebrand factor which is stored in granules and secreted in response to injury helping coagulation. One of its important roles is to promote platelet adhesion to the endothelium in sites of vascular injury. An increased level of vWF indicates endothelial cell dysfunction and it is associated with diabetes, stroke and prothrombotic states (35). When endothelial cells are dysfunctional vWF is released in its complex form which promotes further vessel damage.

Endothelial progenitor cells are important for maintaining vascular integrity due to their contribution to endothelial repair and new vascular formation. They also play a role in supporting integrity of the blood-brain barrier. EPC are stem cells that migrate from bone marrow to the site of ischemia and help repair vascular damage. They have the ability to mature into endothelial cells and are therefore crucial in restoring blood flow after ischemic injury. Higher numbers of circulating endothelial progenitor cells within the first week following stroke have a positive impact on functional outcome (36,37).

Interleukin-6 is a proinflammatory cytokine produced by monocites and endothelial cells. It is involved in development of atherosclerosis. Elevated IL-6 leads to the production of acute phase protein, stimulating leukocyte recruitment and thrombosis (38). Former studies showed that IL-6 is a strong predictor for cardiovascular events and stroke (39). In addition, high levels of serum IL-6 are related to early neurologic deterioration and long-term poor outcome.

Identification and monitoring of biomarkers of endothelial dysfunction could contribute to stroke diagnosis, prognosis and development of therapeutic strategies (40).

Conclusion

Stroke is one of the leading causes of disability and moratility wordlwide. Endothelial dysfunction has an important role in pathogenesis of ischemic stroke. Endothelium regulates homeostasis in the brain, modulates vascular dilatation and constriction by producing cytokines and other mediators. Dysfunction of the endothelium leads to a protrombotic and proinflamatory state which disrupts the blood-brain barrier. Endothelial dysfunction is an important underlying cause of stroke and it has been recognized as one of cerebrovascular risk factors. It is important to detect endothelial targets to protect different cell types in ischemia. Those places can be targets for novel stroke therapies. Modulation of endothelial function is a potential new treatment target in primary and secondary stroke prevention. The value of identified biomarkers remains uncertain. Future studies are needed to search for useful biomarkers. The investigations of biomarkers are important in order to contribute to diagnostic accuracy, discovery of new therapies and predicting prognosis in patients with acute stroke.

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