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Risk Factors for Cerebrovascular Disease (Stroke) in Elderly

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Abstract

The patophysiology of ischaemic stroke includes thrombosis and embolism. The risk factors are divided into two, namely risk factors that can be modified and risk factors that cannot be modified. Risk factors that cannot be modified are age, gender, race or ethnicity, family history of stroke and genetic factors. While risk factors that can be modified are hypertension, diabetes mellitus, hypercholesterolemia, smoking, atrial fibrillation, valvular heart disease, and carotid stenosis. The concept of ischemic penumbra is a basic reference in stroke treatment, because it is a manifestation of the presence of cellular structures of neurons that are still alive and may still be reversible if a rapid treatment is carried out. By understanding the pathogenesis of stroke through the mechanism of cell death, it is hoped that it can detect early and be used as a reference in the development of a policy to take preventive measures and early diagnosis in establishing the diagnosis of cerebrovascular disease

Keyword : *Risk factors CVD, Stroke, elderly*

Abstrak

Patofisiologi stroke iskemik meliputi trombosis dan emboli. Faktor risiko dibagi menjadi dua, yaitu faktor risiko yang dapat dimodifikasi dan faktor risiko yang tidak dapat dimodifikasi. Faktor risiko yang tidak dapat dimodifikasi adalah usia, jenis kelamin, ras atau etnis, riwayat keluarga stroke dan faktor genetik. Sedangkan faktor risiko yang dapat dimodifikasi adalah hipertensi, diabetes melitus, hiperkolesterolemia, merokok, fibrilasi atrium, penyakit jantung katup, dan stenosis karotis. Konsep penumbra iskemik adalah referensi dasar dalam pengobatan stroke, karena merupakan manifestasi dari adanya struktur seluler neuron yang masih hidup dan mungkin masih reversibel jika dilakukan perawatan cepat. Dengan memahami patogenesis stroke melalui mekanisme kematian sel, diharapkan dapat mendeteksi dini dan dijadikan acuan dalam pengembangan kebijakan untuk melakukan tindakan pencegahan dan diagnosis dini dalam menegakkan diagnosis penyakit cerebrovascular

Kata Kunci : Faktor risiko CVD, Stroke, lansia

I. INTRODUCTION

Cerebrovascular Disease (Stroke) in elderly is a global health problem, due to the second cause of death and major disability in almost all countries of the world. This disease has a great impact on the sufferer, the social environment and the economic burden, so it requires great effort for experts to understand the underlying pathogenesis, and strive for the best treatment. Stroke is a global health problem, due to the second cause of death and major disability in almost all countries of the world. This disease has a great impact on the sufferer, the social environment and the economic burden, so it requires great effort for experts to understand the underlying pathogenesis, and strive for the best treatment[1,2]

World Health Organization (WHO) data in 2015 annually 15 million people worldwide suffer from stroke. Globally, stroke is the second leading cause of death over the age of 60, and the fifth cause of death in people aged 15 to 59. Worldwide in 2010, it is estimated that the incidence of ischemic stroke is higher than the incidence of bleeding stroke. The mortality rate of ischemic stroke is 57% in low- and middle-income countries and in bleeding strokes that 84% in low and middle-income countries.[3,4]

These risk factors are divided into two, namely risk factors that can be modified and risk factors that cannot be modified. Risk factors that cannot be modified are age, gender, race or ethnicity, family history of stroke and genetic factors. While risk factors that can be modified are hypertension, diabetes mellitus, hypercholesterolemia, smoking, atrial fibrillation, valvular heart disease, and carotid stenosis.[5] Data from the study The INTERSTROKE Study, which conducted research on stroke risk factors in 84 centers in 22 countries in the world, stated that there are five main risk factors that contribute to the incidence of stroke as much as 80%, namely hypertension, current smoking status, central obesity, diet and physical activity.[3]

II. RISK FACTORS OF STROKE

These risk factors are divided into two, namely modifiable risk factors and non-modifiable risk factors. Risk factors that cannot be modified are age, gender, race or ethnicity, family history of stroke and genetic factors. While risk factors that can be modified are hypertension, diabetes mellitus, hypercholesterolemia, smoking, atrial fibrillation, valvular heart disease, and carotid stenosis.[2,6]

a. HYPERTENSION

Hypertension is the main risk factor both for ischemic stroke and for bleeding stroke. The risk of stroke in people with hypertension is directly proportional to the increase in blood pressure.[5,7]

b. DIABETES MELLITUS

Patients with diabetes, be it type I DM or type II DM, have a higher risk of atherosclerosis. Rancho Bernarod found an increased relative risk of a person with DM to suffer a stroke, which was 1.8 times for men and 2.2 times for women. Data from the Framingham study states that metabolic syndrome, a marker of insulin resistance, has a greater risk of suffering a stroke. Patients with metabolic syndrome and DM have a higher risk of suffering stroke than patients with DM or metabolic syndrome alone.[6,8]

c. DYSLIPIDEMIA

LDL is an important part in the formation of atherosclerosis plaques, because it will undergo oxidation so that foam cel will form. The majority of studies state that there is a

linear relationship between LDL levels and stroke incidence and an inverse relationship between HDL levels and stroke incidence rates. In general, the lipid profile effect has more meaning in coronary heart disease when compared to ischemic stroke.[9]

III. CEREBRAL PERFUSION

Cerebral blood flow (ADO) is the amount of blood going to the brain, which is decisive on perfusion in cerebral. The adult brain uses 20% of the blood pumped by the heart at rest, and in the normal state fills 10% of the intracranial space. The brain is a very metabolically active organ. It has a volume of only 2-3% of the total body, receives 15% of the cardiac output, consumes about 20% of the body's oxygen and 15% of the body's total glucose. ADO strictly regulates the needs of brain metabolism, the average ADO flow is maintained at 50 ml per 100 grams of brain tissue permenit in adult humans. It is very important to maintain ADO within normal limits because too much ADO can increase intracranial pressure so that it can compress and damage brain tissue.[5]

Sudden brain vascularization disorders for example because ischemic can cause a loss of perfusion to the brain in a few seconds to minutes causing the occurrence of ischemic cascades, brain cells in the nuclei of the ischemic region suddenly, this core area is surrounded by areas that still have the potential to experience death as well, this area is known as penumbra or peri-infarction area. The potential for penumbra that is still possible to rejuvenate or be saved from death is what gives rise to studies on changes in physiological processes that occur a few hours or days after a stroke. The presence of collateral around it accompanied by a compensation mechanism in the form of vasodilation, allowing several circumstances to occur.[6] In small blockages, ischemic regions occur in a short time compensated by local collateral and vasodilation mechanisms. Clinically, the symptoms that arise are Transient Ischemic Attack (TIA) that arises can be in the form of hemiparesis that disappears before 24 hours or general amnesia at a glance. When the blockage is rather large, the ischemic area is wider.[1,7]

The decline in regional CBF is greater, but with a compensatory mechanism it is still able to restore neurological function within a few days to 2 weeks. This state is clinically called Reversible Ischemic Neurologic Deficit (RIND). Large enough blockages cause large ischemic areas so that collateral and compensation mechanisms cannot cope with them. In this state arises a continuing neurological deficit.[3]

IV. PATHOGENESIS OF STROKE: MECHANISMS OF CELL DEATH

In broad brain ischemics, inhomogeneous areas appear due to differences in ischemic levels consisting of 3 different layers (areas), namely the core area, penumbra area and areas with excessive perfusion (luxury perfusion). The concept of ischemic penumbra is a basic reference in stroke treatment, because it is a manifestation of the presence of cellular structures of neurons that are still alive and may still be reversible if a rapid treatment is carried out. Efforts to restore the penumbra area are carried out by reperfusion which must be timely so that blood flow back to the ischemic area is not too late, so that the penumbra neurons do not experience necrosis.[1,3,10]

1. DECREASE IN GLUCOSE & HYPOXIA

When there is a disturbance of blood flow to the brain automatically the brain will lack the intake of O2 and glucose for the oxidative phosphorylation process. An anaerobic oxidation process occurs that produces lactic acid. The brain undergoes acidosis, as a result of which protein denaturation occurs, Ca++ influence, glial edema and free radical production occurs. Increased lactate levels are thought to be not only due to anaerobic

metabolism, but also as a result of secondary damage from the expansion of infarction.[11]

In addition, the body's response when glucose decreases and hypoxia occurs is the occurrence of injury reperfusion. It is known that the injury reperfusion process is able to trigger the production of Reactive Oxygen Species (ROS) through the activation of microglia and astrocytes. In response to oxidative processes, the outer membrane of the mitochondria will become more permiable, which can cause the translocation of Bax from the cytosol to the mitochondria and release the cytochrome C. The release of cytochrome C into these mitochondria will stimulate the formation of apoptosomes which will lead to the process of DNA fragmentation. So that many therapeutic studies are directed at preventing the process of apoptosis after ischemic or reperfusion.[11,12]

2. DECREASED ATP

Ischemic stroke is caused by impaired cell energy metabolism and energy failures such as sodium-potassium ATPase. Lack of O2 and glucose will cause ATP depletion so that the Na-K-ATPase pump fails. This will cause the membrane depolarization process so that Na influx occurs. Na enters the intracell carrying Cl- and H2O as a result of which the cell will experience swelling and osmollysis. Energy loss causes ion imbalance, release of neurotransmitters, and inhibition of reuptake of excitatori neurotransmitters such as glutamate.[10,12]

3. OXIDATIVE STRESS

Reactive oxygen species (ROS) are formed due to ischemia mainly after reperfusion of several organ systems including the brain, heart, and kidneys. ROS is usually generated by mitochondria during electron transport, and after ischemic. The high level of Ca++, Na++, and ADP in intracellular will trigger mitochondria to increase the production of excessive oxygen radicals. The production of oxygen radicals is harmful to the brain because levels of endogenous antioxidants (superoxide dismutase (SOD), catalase, glutathione), and antioxidant vitamins (e.g., alpha-tocopherol, and ascorbic acid) usually do not correspond to excessive radical formation.[3] As a result, mitochondria release proteins associated with apoptosis and other constituents within the inner and outer mitochondrial membranes. After tissue reperfusion and oxygenation, mitochondria can produce oxidative stress and MTP formation. Oxygen radicals are also generated during enzymatic conversion such as the conversion of cyclooxygenase-dependent arachidonic acid into prostanoids and the degradation of hypoxanthines, especially after reperfusion. Reactive Oxygen Species (ROS) through the activation of microglia and astrocytes and followed by repeated depolarization and capable of causing blood brain barrier disorders. Changes in nerve and electrolyte excitability that occur suddenly in the early phase of stroke can cause changes in the structure of the nerves in the peri-infarction area so that it can affect the survival of the nerves in the area.[3,6,7]

In addition, free radicals are also produced during the inflammatory response after ischemic. Oxidative and nitrosative stress can be affected by enzyme systems such as superoxide dismutase (SOD) and nitric oxide synthase (NOS). The important role of SOD in cerebral ischemic was shown in studies in rats where by increasing SOD it would reduce injury after cerebral ischemic whereas if it was deficient it would increase injury. Similarly to NOS, the activation of NOS during ischemic increases the production of NO(3)

NOS types I and III are Ca2+ related types and are always expressed, especially in neural tissues (type I) and endothelial cells (type III). The regulation of NOS type II (inducing enzymes) is transcriptionally

mediated by various cytokines. Ischemia results in increased activity of type I and III NOS in neurons and vascular endothelium. At higher stages an increase in NOS type II appears in infiltrated glia cells and neutrophils. In the context of brain ischemia, NOS type I and II are destructive, but the production of type III NOS in blood vessels increases blood flow in the penumbra ischemic through vasodilation and platelet adhesion inhibition, and captures oxygen radicals and has an anti-inflammatory effect through inhibition of leukocyte adhesions on endothelial cells(1)(3). Inhibition of NOS through dimethylarginine asymmetry can lead to a decrease in the bioavailability of nitric oxide associated with vasoconstriction, an increase in free radicals, platelet aggregation and adhesion of leukocytes on the endothelial surface, this process can further worsen the condition of brain ischemia.[10,11]

The interaction of oxygen radicals with other tissue components contributes to the formation of various other radicals. One of the most important is the high and toxic formation of peroxynitrite from superoxide and nitric oxide. Peroxynitrite undergoes spontaneous decomposition to produce hydroxyl radicals. Hydrogen peroxyde is fat-soluble and immediately passes through the cell membrane. Similarly, superoxide crosses the cell membrane through anion channels.[3,6,8] Therefore, distant effects of these two substrates are possible. Whereas hydroxyl radicals are the most reactive oxygen radicals, likely resulting in mostly tissue damage and in very short periods. Free radicals trigger a spectrum of cellular effects including enzyme inactivation, the release of calcium ions from intracellular storage, protein denaturation, lipid peroxidation, cytoskeleton and DNA damage and chemotxis. Mitochondrial function is impaired by free radicals on the inner membrane of the mitochondria and oxidation of proteins that mediate electron transport, H+ extrusion and ATP production. Cytochrome C is released from the mitochondria and provokes apoptosis. Severe oxidative stress results in cell death through necrosis whereas moderate oxidation can trigger apoptosis.[3]

The formation of nitric oxide and reactive free oxygen species is also related to DNA damage and activation of the nuclear enzyme poly-ADP-ribose polymerase (PARP-1). PARP-1 is activated by single-stranded DNA nicks (which may be triggered by oxidative and nitrosative damage) that will consume large amounts of NAD+ to form poly-ADP chains for post-translational modification of a number of enzymes that update PARP-1. It is estimated that the need for NAD+ and ATP depletion leads to cellular energy depletion and cell death. Cell death can be inhibited by inhibiting PARP-1 activity or depleting the PARP 1 gene, suggesting that PARP-1 is a potential therapeutic target.[6,7,13]

V. CONCLUSION

Analysis of risk factors for cerebrovascular disease in the elderly, we can see the distribution of the frequency of risk factors in the elderly. By understanding the pathogenesis of stroke through the mechanism of cell death, it is hoped that it can detect early and be used as a reference in the development of a policy to take preventive measures and early diagnosis in establishing the diagnosis of cerebrovascular disease.

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