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MOLECULAR PATHOLOGY OF CEREBROVASCULAR ATHEROSCLEROSIS

Marsetio Donosepoetro*

ABSTRACT

Cerebrovascular disease are the third most common cause of death in Western countries.

The most frequent manifestation of disease is a sudden episode of neurological deficit termed stroke which is the result of cerebral haemorrhage or cerebral infaction in the mayority of cases.

Stroke secondary to atherosclerosis is most common in people over 50 years old.The incidence of stroke rises dramatically with ages, with the risk doubling with each decade after 35 years old.

About 5 % of people over 65 years old have at least one stroke.

Atherosclerosis is condition where fatty acid deposits occur in the inner lining of arteries and the forming of atherosclerotic plaque,a mass consisting of fatty deposit, and blood platelets.The plaque may obstruct or my trigger clot,a trombus,at that location causing cerebral trombosis.It is called ischemmic stroke.

The basis of the response to injury hypothesis introduced by Russel Ross is that the earliest cellular events that occur during atherosclerosis is a specialized type of chronic inflammatory response to cell injury.

What may begin as a protective inflammatory reponse can become excessive and deleterious to the cell of the artery wall.

The adhesion of leucocytes on endothelial cells and their trans –endothelial migration into intima are mediated by adhesion molecules on the endothelial cell membrane that mainly belong to two protein families:the selectin and the addhesion molecules.

***Key words**: cerebral haemorrhage, selectin and adhesion molecules*

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INTRODUCTION

Cerebrovasular diseases are the third most common cause of death in Western countries. The most frequent manifestation of disease, is a sudden episode of neurological deficit, termed a stroke, which is the result of cerebral haemorrhage or cerebral infarction in the majority of cases. Stroke occurs in 2 per 1000 of the general population. A clinical diagnosis with several pathological causes, is mainly seen in the elderly population.[1]

The clinical diagnosis of stroke, is defined as a sudden onset of non-traumatic focal neurological deficit, that lasts for over 24 hours.The terms minor stroke and reversible ischemic neurological deficit (RIND), are used when recovery of clinical features, occurs after a period of time, usually defined as 7 days. Transient ischemic attacks (TIA), are defined as episodes of non-traumatic focal loss of cerebral or visual function, lasting no more than 24 hours.The causes of stroke can be divided into two main groups: ischemic (85%), caused by cerebral infarction, and haemorrhagic (15%), caused by intracerebral and sub-arachnoid haemorrhage.

All structural components of the brain cell can be targets of ischemic injury: cell coat, plasma membrane, endoplastic reticulum, ribosome, mitochondria, cytoplasmic matrix, nucleus and nucleolus.

Brain ischemia and infarction

The brain is particularly vulnerable to ischemia. Complete interruption of blood flow to the brain, for only 5 minutes triggers the death of vulnerable neurons in several brain regions, whereas 20-40 minutes of ischemia is required to kill cardiac myocytes. Although the human brain represents only 2.5% of body weight, it accounts for 25% of basal metabolism, a metabolic rate 3.5 times higher than that of the brains of other primate species.

Furthermore, central neurons have an exclusive dependence on glucose, as an energy substrate, and the brain stores of glucose and glucogen are limited.

The most frequent manifestation of neurological dysfunction is caused by stroke. There are four types of ischemic stroke: large vessels, small vessels, venous and global. The four main types of ischemic stroke are classified according to the pathogenesis of reduced blood flow to the brain.[2]

Large vessel disease, causes regional infarction, the main mechanism being embolism and thrombosis of cerebral arteries. Infarcts correspond to territories of supply, of cerebral arteries and their main

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branches. Small vessel disease, causes microinfarcts known as "lacunar infarcts". These are caused mainly by atherosclerosis, and predisposed mainly by hypertension and diabetes. Venous infarction that causes haemorrhagic necrosis, is due to thrombosis in a main cerebral venous sinus. Global ischemia causes widespread neuronal necrosis, and leads to laminar cortical necrosis.

The most common lethal brain cell injury is anoxia, that is withdrawal of oxygen from a cell. It is ultimately the most common cause of death among humans, if one considers that vascular occlusion and ruptures, represent the most frequent destroyers of the heart and brain. Hypoxia, a dimished oxygen supply can also be lethal, and it is most caused by diminishing blood supply: *ischemia*.

Stroke secondary so atheroslerosis

Stroke secondary to arherosclerosis, affects about 2 out of 1000 people, or approximately 50% of those who have stroke (stroke related to atherosclerosis). Stroke is the third leading cause of death in most developed countries. Stroke secondary to atherosclerosis is most common in people over 50 years old. The indicence of stroke rises dramatically with age, with the risk doubling with each decade after 35 years old. About 5% of people over 65 years old have had at least one stroke. The disorder occurs in men more often than women.

Atherosclerosis is a condition where fatty deposits occur in the inner lining of arteries, and the forming of an atherosclerotic plaque = a mass consisting of fatty deposits, and blood platelets (thrombocytes).

The plaque may obstruct (occlude the artery by itself), or may trigger a clot, a trombus, at that location, causing cerebral thrombosis (thrombotic stroke) at that location = ischemic stroke. The occlusion of the artery develops slowly. Atheroslerotic plaque does not always cause stroke.[3,4]

There are many small connections among the various brain arteries. If there is enough collateral circulation, even a largely blocked artery may not cause neurological deficits. Risk for stroke secondary to atherosclerosis include: A history of hypertension (present a large part of victims of stroke), peripheral vascular disease, diabetes mellitus, obesity, dislipidemia, hyper homocysteinemia, smoking etc.

Pathogenesis of Atherosclerosis

The Response To Injury Hypothesis: The basis of this hypothesis is that the earliest cellular events that occur during atherosclerosis, is a specialized type of chronic inflammatory response to cell injury. But, what may begin as a protective, inflammatory response, can become exessive, and deleterious to the cell of the artery wall. This is the essence of "The Response To Injury Hypothesis".[3,4]

The first observable events include increased accumulation of lipid and lipoprotein particles beneath the endothelium (sub-endothelial layer), from increased transport and permeability of the endothelial lining cell. This event is rapidly followed by attachment, adherence, and spreading of peripheral blood monocytes and T-lymphocytes, at sites through the arterial tree, particularly at branches and bifurcation. These cells adhere from the formation of adhesive cell-surface glucoproteins, by endothelium and leucocytes, which interact in a ligand-receptor manner.

Thus, one of the earliest changes induced by: hypercholesteremia, hyperglycaemia, hypertension, hyperhomocysteinemia, and also possible by some infection, appears to alter endothelial permeability, together with adherence of leucocytes, representing the first phase of an inflammatory response. But once again, what begins as a protective, inflammatory reponse, later on through the "exessive histo-immunological behaviour" of the vascular wall cells, eventually develops tin a atherosclerosis process.

The leucocytes migrate across the surface of the endothelium, between the junctions of endothelial cells, and are chemotactically atracted into sub-endothelial space, where they begin to accumulate within the intima. Furthermore: in the presence of oxidized low-density lipoproteins (LDL), the monocytes become converted to activated macrophages, and through their scavenger receptors, take up the modified lipoprotein (modified LDL, among others, malondialdehydes), and eventually become foam cells. Foam cells are the first histo-pathological elements within the process of atherosclerosis.

Mechanisms of Injury After Ischemia

Cerebral ischemia may be either transient and followed by reperfusion, or essentially permanent. Within seconds of cerebral ischemia, local cortical activity as detected by electro-encehalography stops.

This massive shutdown of neural activity is induced by K+ efflux from neurons, mediated initially by the opening of voltage-dependent K+ channels and later by ATP-dependent K+ channels, leading to transient plasma membrane hyperpolarization.

A few minutes later, despite this energy sparing response, an abrupt and dramatic redistribution of ions occurs across the plasma membrane, associated with membrane de-polarization (efflux of K+ and influx of Na+, Cl–, and Ca2+).

This "anoxic de-polarization" results in the exessive release of neurotransmitters, in particular, glutamate, promoting further spread of cellular de-polarization, depletion of energy stores, and advancement of injury cascades, through caspases release, the beginning of the process of apoptosis.[4]

Brain ischemia and reperfusion engange multiple independently-fatal terminal pathways involving loss of membrane integrity in partitioning ions, progressive proteolysis, and inability to check these processes, because of loss of general translation competence and reduced survival signal-transduction. Ischemia result in rapid loss of high energy phosphate compounds, and generalized de-polarization, which induces release of glutamate in selective vulnerable neurons, and opening both voltage-dependent and glutamate-regulated calcium channels.[11,12]

Biomarkers of atherosclerosis

The adhesion of leucocytes on endothelial cells and their trans-endothelial migration into the intima are mediated by adhesion molecules on the endothelial cell membrane, that mainly belong to two protein families: the selectin and the adhesion molecules. For the two members of the first group (E-Selectin and P- Selectin), and the two members of the latter group (ICAM-1 and VCAM-1) = (Intercellular Adhesion Molecules, and Vascular Cell Adhesion Molecule), expression has been demonstrated in various cell types, within the process of atherosclerosis, for example in endothelial cells, vascular smooth muscle cells, and macrophages.[10]

Furthermore, recent evidence suggests that atherosclerosis is a chronic inflammatory process.

The concentration of C-reactive protein (CRP)[8], serum amyloid A (Serum Amyloid Antecedant, Acute Phase Serum Amyloid A), also interleukin-6 (IL-6), and soluble intercellular adhesion molecules (sICAM-1) were all increased significantly in men with angiographically documented Atherosclerosis.

Interleukin-6 is produced mainly by activated monocytes and smooth muscle cells (SMC), in atherosclerosis.

Soluble cellular adhesion molecules, such as soluble intercellular adhesion molecules=1 (sICAM-1), are expressed on the surface of activated endothelial cells, in response to inflammatory cytokines, to capture circulating leucocytes, and increase the migration of white cells into the vascular intima.

Another important biomarker, suggested as an early sign of atherosclerosis is the measurement of plasma F2-Isoprostane, a sensitive, specific and noninvasive method for measuring oxydative stress, in clinical setting, where reactive oxygen species (ROS) are involved. F2-Isoprostanes are novel bioactive prostaglandin F-2 like compounds, produced by non-enzymatic free radical-catalyzed, peroxidation of arachidonic acid. Quantification of F2-Isoprostanes has been found to represent a valuable and reliable marker of lipid peroxidation.[11,12]

Another biomarker related to atherothrombosis, is Thrombomodulin, expressed by injured endothial cell, and triggers the onset of thrombosis, attached to the endothelial lining, and later on being a portion of the rupture of the atherosclerotic plaque. Karlheinz Peter at al (1997)[13], reported their findings as follows: Circulating Vascular Cell Adhesion Molecules (VCAM-1) correlates more with the extend of human atherosclerosis, than with other adhesion molecules: ICAM-1, E-Selectin,

P-Selectin and Thrombomodulin.

To evaluate a potential bias on circulating VCAM-1 levels, by the un-equal distribution of factors, such as diabetes mellitus, arerial hypertension, hypercholesterolemia, history of myocardial infarction, and elevation of creatinine, a multivariate regression analysis was performed.

After adjustment for these potential covariates, the correlation between circulating VCAM-1 and atherosclerotic area, wass still highly significant ($p < 0.001$). None of the potential covariates reached a significant level of 0.05.

Thus, the correlation between circulating VCAM-1 and the atherosclerotic area was not due to the bias of unbalanced distribution of the above factors.

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