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Aspirin against Atherosclerotic Intracranial Arterial Stenosis

Hernando Rafael*

Neurosurgeon, Academia Peruana de Cirugía, Lima-PERU

***Corresponding author:** Hernando Rafael, Bélgica 411-BIS, Colonia Portales, 03300 Mexico city, Mexico, Tel: 5255-5264 2774; Fax: 51-991 489 111; E-mail: hrtumi@yahoo.com

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Abstract

There is no doubt that atherosclerosis is a chronic inflammatory disease in the inner wall of the arteries caused by the laws of hydrodynamics and environmental chemicals present into the bloodstream. Atheromatous plaques located at the mouths of the perforating and collateral arteries originated from the supraclinoid carotids, distal end of the basilar artery and the V4 segments of the vertebral arteries, usually cause neurological events of insidious onset, undulating course and progressive. In other cases it can manifest as transient ischemic attacks. For this reason, reducing the size of atheroma in the arteries with mild or moderate stenosis through medical treatment is the goal to follow to cause vascular recanalization and thus, increase the blood flow in the ischemic areas. Therefore, an anti-inflammatory therapy is indicated against atheroma formation.

Previous clinical results suggest that high doses of aspirin are required to prevent or reduce the formation of atheromatous plaques, due to their anti-inflammatory, anti-platelet and anti-thrombotic effects. While in patients with severe stenosis and/or thrombosis in the perforating and small arteries, omental transplantation is indicated, because this tissue causes revascularization in the underlying and adjacent areas to the omentum. In conclusion, without vascular recanalization or revascularization in the ischemic zone, no neuronal regeneration or neurogenesis occurs.

Keywords: Laws of hydrodynamics; Environmental pollution; Atheromatous plaques; Intracranial arterial stenosis; Aspirin; Resveratrol

Introduction

To date, almost all researchers conclude that neurological diseases such as aging, Type 2 diabetes mellitus(early stage), neurogenic hypertension (main representative of essential arterial hypertension), Huntington´s disease (HD), Alzheimer´s disease (AD), Pick´s disease, Parkinson´s disease (PD), Amyotrophic lateral sclerosis (ALS) and Olivopontocerebellar atrophy (OPCA); all of them are of etiology unknown.

On the contrary, based on clinical and neurosurgical experiences [1-8], my colleagues and I believe that these diseases have ischemic origin, because its revascularization by mean of an omental transplantation can cure or improve these disorders. Ischemic process is caused by intracranial atherosclerosis and associated with vascular anomalies at the affected zones of the brain [9-14]. For example, we have operated on patients with familial HD and AD, and after surgery, we observed neurological improvement [3,8].

For this reason, in this review article I will discuss the pathogenesis of atherosclerosis and its medical treatment with aspirin, because previous clinical experiences suggest that is possible prevent and/or reduce the atherosclerotic arterial stenosis [15-25]. I will not comment on the clinical data of patients with severe stroke at major intracranial arteries such as carotids.

Pathogenesis of atherosclerosis

Atherosclerosis, is a chronic inflammatory disease in the inner wall of the arteries [26-29], which is the result of primary and secondary factors [30,31].

Primary factor: It is related with the laws of hydrodynamics in development of atherosclerosis [30,32-35]. During the embryonic stage (about 10 weeks) as soon as the blood begins to flow through the definitive arteries (aorta, brachiocephalic and left subclvian arteries) and its branches; fatty streaks appear in different zones of the intima (composed by three layers: endothelial, subendothelial and internal elastica). This intimal dysfunction in the arterial wall has centrifugal course from the embryonic or fetal aortic arch toward the descending aorta, innominate artery, left subclavian artery, and its terminal and collateral branches. The predilection of the aortic arch for atherosclerotic changes appears to be determinated by the increased velocity of the blood flow and the reduced static pressure or suction effect in this region [30,34,36-38]. In fetal stage, the blood flow in the straight vessels is normally laminar, whereas in adult stage almost always is turbulent because ateroma [30,32,33].

Mechanical stress generated by hemodyamic factors provoke a reactive biological response in the intima from its endothelial layer to the basement layer adjacent to the media, due to a progressive decline of the vasa vasorum in the intima [29,34,37,39]. The distribution of atherosclerotic lesions indicates strongly that there are certain points of predilection. Such points are determinated by the nature of the motion of fluid, in this case the blood [30,34]. These are areas characterized by curvatures, bifurcations, branching, external attachment or tapering. Such locations are subject to a relative decrease in lateral pressure in accordance with the laws of hydrodynamics such as Bernoulli´s

theorem, Poiseuille´s law, Darcy´s law and law of Laplace [28-30,32,33].

Therefore, with the progression of age, the velocity of pulsatile blood flow decrease gradually from the aortic arch, due to a gradual loss of elastin and collagen fibers replacement [31,40,41]; whereas the flow of blood in the coronary arteries is intermittent as a result of systolic contraction [30]. In consequence, this primary factor is almost impossible to control, because anyways would be a response in the inner wall of the arteries to mechanical stimulus generated by the laws of hydrodynamics. In other words, atherogenesis is a histopathological response of the intima to repair the inner wall of the arteries caused by changes in the blood flow and quality of blood.

Secondary factors: Are all agents that increase even more, the damage in the inner wall of the arteries .These factors are a multitude of agents such as the carbon monoxide, volatile organic solvents, smoke and dust, cigarette smoke, insecticides, pesticides, terokal, high ozone levels, sodium hypochlorite, chronic alcoholism, obesity, diabetes mellitus, dehydration, hypotestosteronemia, hyperlipidemias, hypercholesterolemia, hyperglycemia, apolipoprotein E, arterial hypertension, metals (lead, mercury, iron, zinc and manganese, among others), sulfur, benzene, nitrous oxide, some drugs and other environmental pollutants [28,34,36,42-45]. Unlike the primary factor, these risk agents could be prevented and treated in order to reduce the formation of atheromatous plaques [46-58].

In Figure 1, I schematize the direct damage of the ischemic process by atherosclerosis and environmental chemicals in cells throughout the body, especially in neurons of the nervous system, monoaminergic nuclei and islets of Langerhans [3-5,59-62]. Both factors cause intracellular events such as formation of free radicals, continued by oxidative stress, neurodegeneration and finally, cell death [3,59]. Antioxidant defences (or endogenous antioxidants) that prevent oxidative stress are also reduced in these ischemic areas. Thus, atherosclerotic plaques are essentially caused by the laws of fluid dynamics and some risk factors, while cell damage throughout the body is caused mainly by environmental toxins present in the bloodstream and within the cytoplasm cell.

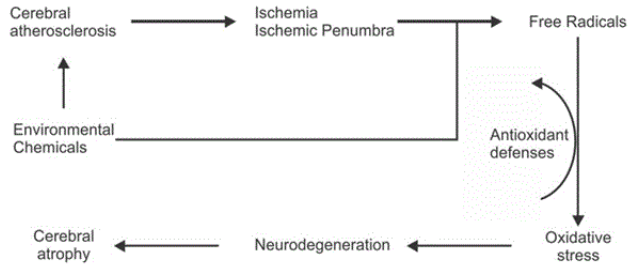

Figure 1: Ischemic events occurred by arterial stenosis, in the intraparenchymal territory of the perforating and collateral arteries originated from the supraclinoid carotids, circle of Willis, basilar artery and V4 segments of the vertebral arteries. The oxidative stress is caused by imbalance between the oxidant and anti-oxidant systems [59].

The earliest atherosclerotic lesions are formed at certain sites of predilection as curvatures, bifurcations and branching. The pathology involves chiefly the intima from its endothelial layer to the basement layer adjacent to the media. This local reaction consists of a reparative process and a thickening due to the proliferation of endothelial cells, leukocytes and macrophages from the subjacent layers and thus, the thickening of the intima gradually projects into the arterial lumen [26,28,30,39,40]. The incidence, location and degree of atherosclerosis is related chiefly with the age and environmental pollution. Since the fourth to the sixth decades of life, intracranial atherosclerosis is considerably more frequent and severe in older adults[36,40,41,63]; especially in the carotid siphon ,the distal end of the basilar artery and the V4 segments of the vertebral arteries [40,63-65].

In embryonic or fetal stages, from the appearance of fatty streaks in the aortic arch until the formation of atheromatous plaques in the aorta and its branches, these plaques are composed of endothelial cells, leukocytes, foam cells, lipid pools, smooth muscle cells, macrophages, platelets, fibrous tissue, cholesterol, fibrolipids, monocytes, fibrin, necrotic core, calcium, elastic tissue and collagen, among other components [26-28,30,36,39,66,67]. Therefore, the formation of these atheromatous plaques in the inner wall of the arteries is the result of local or diffuse inflammatory processes caused by hemodynamic factors and environmental chemicals. Besides this, inflammatory cytokines released into the bloodstream from adipose tissue [5]; the macrophages, monocytes, and T-Cells into the intima also have the ability to produce inflammatory cytokines as nuclear factor kappa-B (NF-kB), I kappa B kinasa beta (Ikk-beta) kmonocyte chemoattractant protein-1 (MCP-1), metalloproteinases (MMP), tumor necrosis factor-alpha (TNF-alpha), transforming growth factor-beta (TGF-beta), proteolytic enzymes, platelet-derived growth factor (PDGF) and Insulin-like growth factor-I (IGF-I) [26-28,62,67,68].

Likewise since the fetal stage and throughout adult life, endothelial cells (all endothelial cells in the arteries and capillaries have insulin receptors, as well as mainly glucose transporter-1, GLUT-1) in the inner wall of the arteries, in tissue and organs [5,69]; they all suffer metabolic (formation of free radicals and oxidative stress) and degenerative changes, and finally, cell death [46,51-54,59,70-74]. The cytotoxic effects of various environmental chemicals within cells (or neurons) are capable proteins and DNA damage [44,48,50,51,54,57,58] and therefore cause local or diffuse atrophy in the brain ,as well as in other organs, but related also with the anatomical variants of the arteries [7,8,60,75-77]. Then, atherosclerosis is a lipoprotein-driven disease that leads to plaque formation at specific sites of the arterial tree through intimal inflammation [28,29]. In other words, atherosclerotic plaques form in response to an injury of the intima.

Size of atherosclerotic plaque and their effects

Arterial stenosis: It is the partial occlusion of the artery commonly caused by atheromatous plaques. The degree of stenosis can range from mild, moderate or severe [2,26,27,30,39,41,63-65]. Therefore, the reduced blood flow is also variable in certain zones of the brain, causing likewise varying degrees of ischemia and ischemic penumbra. Tomographic and neurosurgical observations in patients with aging, type 2 diabetes, neurogenic hypertension, HD (Figures 2A and 2B), Pick´s disease (Figure 3) AD, PD, OPCA (Figure 4) and ALS have shown that in all of them there are cerebral atherosclerosis, associated to vascular anomalies [3,6,9,12,78,79]. The atheromatous plaques are located at the mouths of origin of the collateral (ophthalmic, posterior communicating and anterior choroidal arteries) and anterior perforating arteries originated from the supraclinoid carotids and circle of Willis; the posterior perforating arteries originated from the basilar bifurcation and mesencephalic arteries; the superior cerebellar arteries, pontine arteries and anterior inferior cerebellar arteries

originated from the basilar artery, and the anterior-ventral spinal arteries, posterior inferior cerebellar arteries and some perforating arteries originated from the V4 segments of the vertebral arteries [3,4,6-8,60,64,76,78,80-82]. For example, the aging process is caused by progresive ischemia in the producing hypothalamic nuclei of growth hormone–releasing hormone (GHRH), especially in the arcuate nuclei [1,78,83,84]. AD is caused by ischemia in the medial temporal lobes and subcommissural regions [78,80] and PD is caused by ischemia in the subthalamus, zone incerta, ventral lateral nuclei of the thalamus and substantia nigra [3,78].

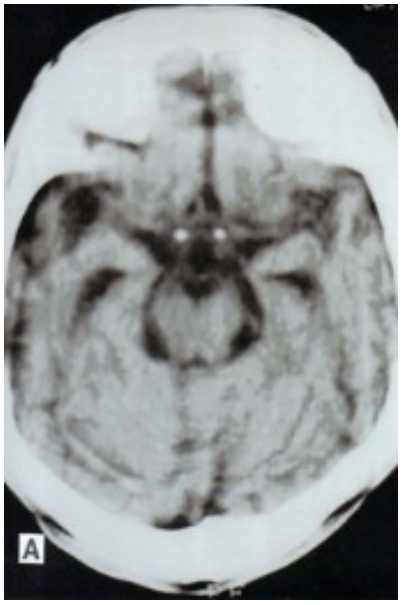

Figure 2A: CT scan without contrast showing atherosclerosis at the circle of Willis and its terminal branches, in a 35 year old man with familial HD [8].

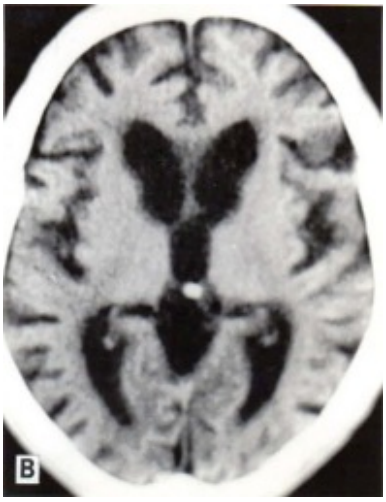

Figure 2B: CT scan without contrast showing severe cerebral atrophy, dilatation of the III ventricle and severe atrophy in the head of caudate nuclei, in the same patient with familiar HD [8].

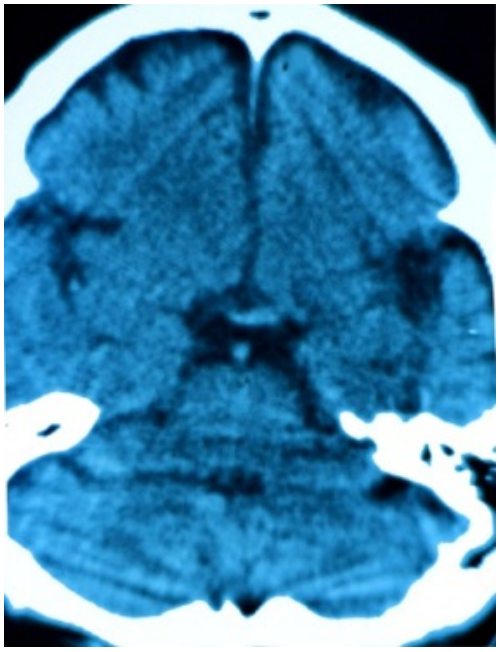

Figure 3: CT scan without contrast showing atherosclerosis at the supraclinoid carotids, basilar artery and moderate atrophy in both frontal and temporal lobes, in a 59 year old man with Pick´s disease [79].

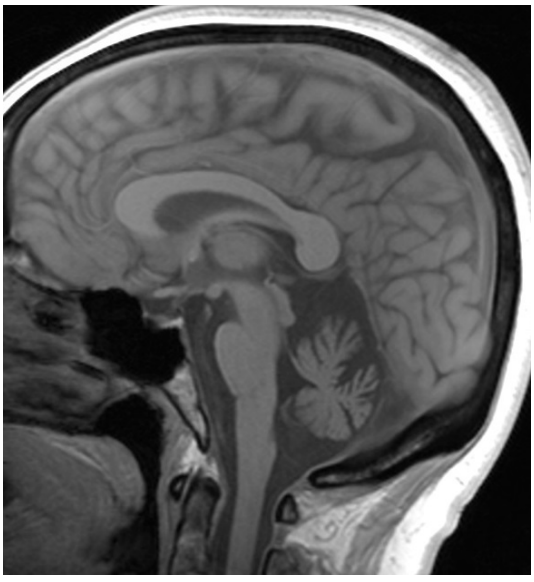

Figure 4: MRI scan without contrast showing severe cerebellar atrophy in a 61 year old woman with neurological history of OPCA by three years. In addition, this patient has atherosclerosis at the basilar artery and V4 segments of the vertebral arteries.

The clinical onset in all the above-mentioned diseases is insidious, undulating course (alternating periods of improvement and worsening) and progressive, and in other cases, it can manifest as mini

strokes or transient ischemic attacks. In later stages, this ischemic process in the intraparenchymal territory causes local or diffuse brain atrophy [3,8,60,74,78,83,84]. In all these diseases the diagnosis is clinical and by contrast, imaging studies (CT, MRI, SPECT or PET) are of little help [2,6,8,78,83].

Arterial thrombosis: It is the complete occlusion of the arterial lumen by atheromatous plaques located at the mouths of origin of the perforating arteries (less than 1 mm in diameter) [12,14,82], as well as in small arteries (collateral branches); both of them arterial branches originated from the supraclinoid carotids, circle of Willis and vertebro-basilar system. The distal parenchyma to the thrombosis, rarely is followed by edema, but by atrophy in the affected area [1,76,80,81,84-86]. The stenosis and/or thrombosis at the arterial branches originated from the V1 and V2 segments of the vertebral arteries can cause cervical degenerative disease and later on, cervical spondylotic myelopathy [87-89]; while the stenosis at the mouths of origin from the anterior-ventral spinal arteries or its perforating branches cause the bulbar form of ALS [3,6,76].

On the contrary, thrombosis in the carotid (C1 to C4 segments) and vertebral (V3 or V4 segments) arteries or its terminal branches causing more serious neurological pictures due to ischemic infarction and edema, which in many cases are fatal [81,83-85]. For example, thrombosis in the M1 segment of the middle cerebral arteries can cause ischemic infarction, edema, transtentorial herniation of temporal lobes into tentorial notch and later on, it provoke central herniation of brainstem through notch.

Arterial thromboembolism: Atherosclerotic plaque rupture (or erosion) with distal luminal thrombosis is the most common mechanism responsible for the majority of acute carotid or vertebro-basilar syndromes. The portion of atheromatous plaque detached is integrated by a fibrous cap and necrotic core [26-28,36,39,54]. The repair of intraplaque bed occurs by vasa vasorum, which invades the intima from the adventitia as the intima enlarges.

So that, like the arterial thrombosis, this form of thromboembolism can also cause mild to severe neurological pictures by occlusion into the distal arterial segments to the origin of the thrombus. Treatment is medical and/or neurosurgical. Atherosclerotic plaque rupture with luminal thrombosis is the most common mechanism responsible for the majority of acute cerebral and coronary syndromes.

Medical treatment of atherosclerotic arterial stenosis

Based on above-mentioned data there is no doubt that atherosclerosis is clearly a chronic inflammatory disease in the inner wall of the arteries, which appears since the intrauterine life and progresses with age. About 30 years of age and more, we found different grades of atherosclerotic plaques in the supraclinoid carotids, the basilar bifurcation and the V4 segments of the vertebral arteries demonstrated by imaging studies , neurosurgical and autopsy findings [1,2,4,8,40,41,63,64,66,87,88].

Accordingly, these atherosclerotic plaques located at the points of bifurcation of the terminal and collateral branches from the aorta (innominate artery, left subclavian artery, carotid arteries, vertebral arteries ,intercostal arteries, celiac trunk, mesenteric and renal arteries, iliac arteries and median sacral artery), as well as at the mouths of origin of the perforating arteries; all of them can provoke ischemia, ischemic penumbra, and/or infarcts in affected areas and organs [1,2,5,6,23,30,64,89-91]. By contrast, based on the anti-inflammatory, anti-platelet and anti-thrombotic effects of aspirin, several encephalic zones can experience neurological improvement by vascular recanalization (increase blood flow in existing arteries) into patients with arterial stenosis [5,15-18,22,90,92]. Due to a reduction in size of atheroma and recovery of the blood flow in the ischemic areas. Likewise, the entry of nutrients and oxygen would favor synthesis of endogenous antioxidants such as superoxide dismutase, catalase and glutathione peroxidase [78,93]. Similarly, exogenous antioxidants such as resveratrol, vitamin A, Vitamin C and Vitamin E, among others [94,95], they may also enter into ischemic areas. On the contrary, without aspirin, the result would be negative into patients with stenosis at the mouths of origin of the perforating and collateral arteries, which vascularized the brainstem. On the other hand, aspirin can also prevent the formation of intracranial aneurysms [67,68,96].

The mechanism of action of aspirin occurs through permanent inactivation of cyclo-oxygenase-1 (COX-1) and cyclo-oxygenase-2 (COX-2) enzymes, which catalyze the conversión of free arachidonic acid to prostaglandin-H2, a substrate for several downstream isomerases that generate bioactive prostanoids, including thromboxane A2 (TXA2) and prostacyclin [25,97,98]. High doses of aspirin (300 mg or more per day) are needed to inhibit COX-2 than to inhibit COX-1. These differences partly account for the need to use higher aspirin doses to achieve analgesic and anti-inflammatory effects [15], where anti-platelet effects can be obtained with daily doses as low as 30 mg [97]. Moreover, aspirin has anti-thrombotic effects due to inhibition of cyclo-oxygenase enzymes in platelets, which reduces the extent of TXA2 (a potent vasoconstrictor and platelet agonist) formation and consequently the agreeability of platelets [25,99-101]. In this way the formation of intra-arterial thrombi is thus reduced.

In addition to this, aspirin, as well as other non-steroidal anti-inflammatory drugs(NSAIDs) (ibuprofen, diclofenac, ketoprofen, naproxen, etc.) also directly inhibits to inflammatory cytokines, proteolytic enzymes and growth factors secreted by macrophages, monocytes, and T-cells located in the atherosclerotic plaques [25-28,62,67,68,101]. That is, aspirin causes a reduction of inflammatory molecules such as TNF-alpha, PDGF, TGF-beta, metalloproteinases and NF-kB, among others [5,22,67,95]. Other studies also suggest that resveratrol decreases the serum levels of NF-kB, TNF-alpha and COX-2 enzym [94,95].

Therefore, through these actions, aspirin is the drug that can reduce the size of atheromatous plaques and prevent the new growth of atheroma; especially in the arteries of small and moderate calibre [23,25,101,102], as well as at the mouths of origin of perforating arteries that vascularized the brainstem (diencephalon, midbrain, pons and medulla oblongata). Therefore, aspirin is the drug of choice for the prevention and treatment of several challenging diseases (in early stages) such as stroke [22,86,90], aging [1,84,103], type 2 diabetes [5,15], neurogenic hypertension [2,15,59], aneuryms [67,68], PD [16,18], AD [3,59,83] and ALS [6,76], among other diseases. Clinical data suggests that other drugs whose platelet anti-aggregant effects are achieved through different mechanisms of action have been developed, such as clopidogrel [17,25,102], cilostazol [24], ticlopidine and dipyridamole, which do not inhibit COX-1.All of them, in combination with aspirin, have better effect than aspirin alone [24,25,102,103]. Likewise, in my opinion, we can use the combination of aspirin with reveratrol [5]. On the other hand, clinical results suggest that aspirin can improve blood flow in the intraparenchymal territory of the exocrine and endocrine pancreas, kidneys and bowels, due to vascular recanalization [5,91,96,104,105]. Therefore, by increasing blood flow, aspirin could improve the function of the islets

of Langerhans in the pancreas, kidney nephrons and cells of the intestinal wall. However, the use of aspirin should be associated with vitamin K, to reverse the damaging effects of aspirin on blood clotting. Vitamin K is found mostly in green leafy vegetables as lettuce, spinach, broccoli, cauliflower, turnips, etc. Based on the above data, we have transplanted omentum on the optic chiasm, hypothalamus, interpeduncular fossa and anterior surface of the medulla oblongata, into patients with severe stensosis and/or thrombosis [1-6].

Finally, recently the World Health Organization (WHO) reported that about 23% of global deaths per year are attributed to environmental toxins such as air pollution, the water and soil, the exposure to chemicals, climate change and ultraviolet radiation. According to WHO cerebrovascular and heart diseases, they are the most affected in the elderly. For example, in Mexico city air quality is fair or poor due to environmental pollution, especially by high ozone levels in winter and/or spring. Therefore, the government enacted measures to reduce the number of motor vehicles and prevent fire between major. That is, air quality and the use of toxic substances can be reduced only by government programs and education to society. The digestive and respiratory systems are the first to suffer damage and later, these environmental pollutants can be measured in the blood [53].

Conclusion

There is no doubt that atherosclerosis is a chronic inflammatory disease in the inner wall of the arteries, due to the influence of primary and secondary factors. The first is related to the laws of hydrodynamics, while secondary with environmental pollutants measured in the blood .Both factors cause damage in the intima of the arteries (atherosclerosis) and direct injury to every cell in the body, particularly in neurons of the brain.

Therefore, based on their anti-inflammatory, anti-platelet and anti-thrombotic actions of aspirin and to a lesser extent other NSAIDs at the point of arterial stenosis by atheroma in the perforating and small arteries, the residual nervous tissue in ischemia and ischemic penumbra can improve upon receiving an increased blood flow, oxygen and other nutrients and thus, facilitate the synthesis of endogenous antioxidants and neuronal regeneration. That is, without vascular recanalization or revascularization to the ischemic zones, residual neurons no re-send axons to specific areas already established.

Then vascular recanalization could allow the entry of exogenous antioxidants, vitamins and minerals to improve function of the residual nervous tissue .While into patients with severe stenosis and /or thrombosis at these small arteries, an omental transplantation is indicated, because this tissue cause revascularization in the affected area and surrounding zones. That is, through these neovessels, the ischemic parenchyma receives an increase in blood flow, oxygen, neurotransmitters, growth factors, cytokines and omental stem cells. However, greater numbers of controlled clinical studies are needed to confirm our observations in patients with early symptoms of AD, HD and PD, among other diseases.

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