

Moya Moya Disease Patho-Physiology, according to Quantum Biophysical Semeiotic. The central role of Mitochondrion Heritable Impairment (CAEMH) in Angiogenesis.

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The aim of this article is to demonstrate the existence of Moya Moya Disease Inherited Real Risk, present in all mothers of patients suffering from Moya Moya Disease (MMD). The disease is dependent on Congenital Acidosis Enzyme-Metabolic Histangiopathy, a mitochondrial disease transmitted from the mother, *conditio sine qua non* of the most serious and deadly disorders.

At present, the best therapy of MMD is its Pre-Primary Prevention with Reconstructing Mitochondrial Quantum Therapy.

Moya Moya disease is an uncommon cerebrovascular condition characterized by the progressive stenosis of bilateral, less frequent unilateral, internal carotid arteries with compensatory formation of an abnormal network of perforating blood vessels providing collateral circulation (1- 7).

The etiology and pathogenesis of Moya Moaya Disease disease (MMD) is till now unclear while its diagnosis only recently has become clinical, quick and easy (7).

In following I suggest a new patho-physiological theory, based on the miochondrion heritable impairment, I have discovered 37 years ago, termed Congenital Acidotic Enzyme-Metabolic Histangiopathy (CAE-MH), underlying the cause of vascular anomalies, characteristic of MMD (7-16).

Because they ignore Quantum Biophysical Semeiotic Inherited Real Risk of MMD, some Authors state that familial Moya Moya disease has been noted in as many as 15% of patients, indicating an autosomal dominant inheritance pattern with incomplete penetrance. Genetic analyses in familial MMD and genome-wide association studies represent promising strategies for elucidating the pathophysiology of this condition (6).

In this paper, genetic factor, i.e., MMD Inherited Real Risk, analyzed from Quantum Biophysical Semeiotic view-point, is outlined. This research directions promise not only to offer new insights into the origin of MMD, but to enhance our understanding of new vessel formation in the CNS, aiming to provide Physicians a new, efficient Pre-Pimary and Primary Prevention, as in all other Inherited Real Risk (8-12).

Progressive bilateral or unilateral stenosis of the internal carotid artery with frequent involvement of the proximal anterior and middle cerebral arteries is characteristic of Moya Moya disease. Histopathological studies of affected internal carotid artery segments in MMD demonstrate eccentric fibro-cellular thickening of the intima, proliferated SMCs, prominently tortuous and often duplicated internal elastic lamina, with no inflammatory or atheromatous involvement (6).

Te above-mentioned arterial vessel alteration, causing Microcirculatory Activation, type I, associated, of microcirculatory units of frontal-parietal and temporal regions, really brings about also Low Grade Chronic Inflammation, detected by the refined, reliable Quantum Biophysical Semeiotic Method (7, 13).

Vessel occlusion results from excessive accumulation of SMCs and thrombosis within the lumen. It is hypothesized that in the setting of arterial stenosis or occlusion, hypoxic regions of the brain induce collateralization through the formation of dilated and tortuous perforating arteries.

Histopathologically, the Moya Moya collateral vessels display thinned media with fibrin deposition in the vessel walls, fragmented elastic laminae, and microaneurysm formation (6). This native revascularization strategy is orchestrated by the expression of various growth factors involved in angiogenic signaling cascades, including HIF-1, VEGF, bFGF, transforming growth factor- β_1 , hepatocyte growth factor, and MMPs (6).

Taken together these studies indicate the existence of a proangiogenic intracranial milieu in patients with MMD, as the following experimental evidence, referred in my previous article, suggests (7). In health, digital pressure of mean intensity (700 dyne/cm.²), applied on large artery (e.g., brachial artery) brings about *simultaneously* Microcirculatory Activation, type I, associated, in the distal, peripheral microcirculatory-tissue units, playing a central role in bedside diagnosis. As a matter of facts, Moya Moya disease bedside diagnosis is based on such a microcirculatory activation, brought about by carotid vessels and Willi's circle heritable stenosis.

Future studies will also aim to develop genetic and serum biomarkers that corroborate my clinical theory, created with the data collected with the Psychokinetic Diagnostic (14, 15), demonstrating the hub role played by Congenital Acidotic Enzyme Metabolic Histangiopathie (16).

Really, Moya Moya is a neurological disease sometimes difficult to differentiate, in its early stage, from mitochondrial disorders in children when non-traumatic ischemic stroke is considered (17). Interestingly, it is well known the relation between mitochondrial impairment and angiogenesis, I have demonstrated, for instance, as regards the Campbell De Morgan spots, skin typical sign of CAEMH (18).

Angiogenesis is a dynamic and energy-consuming process, requiring endothelial cells to switch from a quiescent state to a migratory and proliferative phenotype in order to support the formation of new blood vessels. Although proximal to blood, endothelial cells are utilize anaerobic glycolysis as an energy source to the detriment of mitochondrial oxidative phosphorylation. Notoriously there is a small amount of mitochondria in endothelial cells . In this context, endothelial mitochondria have emerged as signaling hubs that modulate a wide range of endothelial functions, including angiogenesis, by coordinating reactive oxygen species and calcium signaling, metabolism and apoptosis (19). As a consequence, Authors focus on recent findings identifying mitochondrial targeting compounds that exhibit pro-angiogenic or anti-angiogenic properties, and could therefore be of clinical importance for the treatment of vascular pathologies (19).

Interesting for my hypothesis is a research in which the decreased expression of vascular endothelial growth factor (VEGF) in the renal tubules is thought to cause progressive loss of the renal microvasculature with age (20).

Mitochondrial dysfunction may be a principal phenomenon underlying the process of aging. The relation between VEGF expression and mitochondrial dysfunction in aging is not fully understood, because CAEMH is still largely unknown. If mitochondrial dysfunction blocks VEGF expression than it contributes to impaired angiogenesis in the aging kidney (20).

VEGF are able to modify endothelial cell phenotype. Under physiological or non-pathological conditions, endothelial cells remain quiescent under a balance of pro- and anti-angiogenic factors. When pro-angiogenic factors dominate, endothelial cells quickly switch to angiogenic phenotypes that are categorized as either migratory tip cells or proliferating stalk cells (21). Although research

on angiogenesis has revealed key mechanisms that regulate tissue vascularization, therapeutic success has been limited owing to insufficient efficacy, refractoriness and tumor resistance (22).

Emerging concepts suggest that, in addition to growth factors, vascular metabolism also regulates angiogenesis and is a viable target for manipulating the microvasculature. Recent studies show that endothelial cells rely on anaerobic glycolysis for ATP production, and that the key glycolytic regulator 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3 (PFKFB3) regulates angiogenesis by controlling the balance of tip versus stalk cells (22).

As endothelial cells acquire a tip cell phenotype, e.g., due to local acidosis as it appears in localized area of individual with intense CAEMH, they increase glycolytic production of ATP for sprouting. Authors report a detailed description of a family affected by a hereditary multisystem disorder associated with moyamoya syndrome (23).

In my opinion, the mother transmit via mitochondria the Inherited Real Risk of MMD, rather than the disease itself.

The QBS symptomatology of MMD Inherited Real Risk, bedside diagnosis is based on, consists of:

- A) reduced Latency Time of Ocular-Gastric Aspecific Reflex: 4-5 sec. (NN = 8 sec.). Its intensity is significantly higher than the normal one: 4 cm. *versus* 2 cm.;
- B) reduced Latency Time of parietal-, temporal-, frontal- Brain area-Gastric Aspecific Reflex: 5-6 sec. (NN = 8 sec.). Interestingly, the intensity of the reflex is also higher than the normal one: 4 cm. *versus* 2 cm.. In occipital and cerebellar areas microcirculation is apparently physiological; Latency Time of brain- gastric aspecific reflex is normal, i.e., 8 sec, but the Duration is 4 sec. (NN > 3 sec.-4 sec <9
- C) in all above-mentioned brain areas there is Microcirculatory Activation, type I, associated (7), whose intensity increases with the passing of the years from birth;
- D) in the above-mentioned cerebral convolutions there is Low Grade Chronic Inflammation (LGCI), as in all other cases (24). The evaluation of LGCI allows doctor to recognize the stage of disease, paralleling the seriousness of underlying disorder.

In overt MMD all signs are worsened, in relation to the stage of disease. Women, apparently healthy, but involved by MMD Inherited Real Risk, before the beginning of a pregnancy, must initiate the Reconstructing Mitochondrial Quantum Therapy, under accurate therapeutic monitoring to personalize the treatment (25).

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