

QBS Inherited Real Risk of epilepsy: physiopathology, diagnosis and primary prevention

Stagnaro S.
Caramel S.
Marchionni M.

Abstract

The comprehension of the pathogenesis of epilepsy finds a new impulse in studies on nonlinear dynamics of EEG signals and in the growing genetic molecular evidence of the mitochondrial origin of this disease. These data are consistent with the information registered bedside by Quantum Biophysical Semeiotics that clinically investigates microcirculation, both on a functional viewpoint (by studying deterministic chaotic dynamics) and on a structural viewpoint. Microcirculatory dysfunctions reflect those of a genetically altered mit-DNA and of a functional mitochondrial cytopathy known as Congenital Acidotic Enzyme-Metabolic Histangiopathy originating from this mutation and which is particularly intense both in patients with epilepsy and in those with an Inherited Real Risk of epilepsy. Preclinical diagnosis of an Inherited Real Risk of epilepsy allows to finely select subjects with a predisposition to this disease since birth in order to perform an efficient pre-primary and primary prevention.

Introduction

The complex pathogenesis of epilepsy has not yet been fully explained in a unique, consistent and harmonic form according to a shared scientific opinion. The terminology variants proposed for epilepsy by various Authors does not make this achievement easier. The result is that literature includes different approaches which do not seem to have a reciprocal connection.

During the past decades scientists have tried to explain epilepsy as a primary metabolic disorder. According to the actual scientific knowledge, the latest ring of each metabolic or biochemical influence able to modify predisposition to epilepsy is the polarization level of the neuronal membrane, i.e. the difference in potential between the inside and the outside of a cell. From now on, this highlights the important role of the mitochondrion in the etiopathogenesis of epilepsy.

Many metabolic factors can influence this target. The polarization level of the neuronal membrane is maintained by active transfer of ions, especially the sodium, calcium and potassium ions. Sodium ions are continuously transferred outside the membrane thanks to a mechanism known as "sodium pump". Sodium, in turn, is exchanged by potassium by means of ATP-dependent channels. The main source of the energy required to ensure the membrane gradient is the process of glucose oxydation, and therefore the mitochondrial Redox activity.

Membrane depolarization can originate from a relative impairment in the sodium pump causing an accumulation of sodium ions inside the neuron in case of a non-physiological free energy level. The membrane can also be depolarized, repolarized and hyperpolarized under the action of excitatory and inhibitory synapses. Epileptogenic biochemical agents can interfere with any of these basic mechanisms of neuronal membrane polarization. This explains, for example, why the epileptic threshold can lower if certain pathological conditions reduce oxygen and/or glucose supply to nervous tissues. Both substances are essential for the metabolism which supplies the energy for active ion transfer.

The sodium-potassium pump, also called ATP-dependant Na^+/K^+ (Na^+/K^+ ATPase) pump, is an enzyme located in cellular membranes. It is ATP-dependant, and therefore strictly related to mitochondrial activity. For this reason, epilepsy is supposed to be a mitochondrial disease in some studies. Mitochondrial dysfunctions cause cellular suffering, also known as mitochondrial cytopathy. Mitochondrial cytopathies [1] are the basis of mitochondrial diseases, which are often caused by mutations, acquired, or maternally inherited in the mitochondrial DNA or nuclear genes that code for respiratory chain complexes in mitochondria. Mitochondrial cytopathies represent a heterogeneous group of multisystem diseases which preferentially affect the muscle and nervous systems. Today, approximately 200 different diseases caused by mutations of mitochondrial DNA (mit-DNA) are known. Owing to the non-uniform distribution of mitochondria in tissues and the co-existence of mutated and wildtype mit-DNA (heteroplasmy) in these organelles, these disorders may present with a huge variety of symptoms, even though the same mutation is involved. There is compelling evidence for the direct involvement of mitochondria in certain neurodegenerative disorders, such as Parkinson's disease, Friedreich's ataxia (FRDA), amyotrophic lateral sclerosis (ALS), Huntington's disease, myoclonic epilepsy and temporal lobe epilepsy (TLE). This suggests that the critical factor which determines the survival of neurons in neurodegenerative disorders is the degree of mit-DNA damage and the maintenance of an appropriate mit-DNA copy number [2, 3]. Mitochondrial diseases involve multiple organs and show heterogeneous and unpredictable progression. The most common clinical presentation of mitochondrial diseases is encephalomyopathy, and epileptic seizures can frequently occur as a presenting sign of mitochondrial encephalopathy. Whether mitochondrial dysfunction or epilepsy is the cause or consequence is still debatable. Epileptic phenotypes vary in different mitochondrial diseases [4]. Oxidative stress and mitochondrial dysfunction are contributing factors to various neurological disorders. Recently, there has been increasing evidence supporting the association between mitochondrial oxidative stress and epilepsy. Although certain inherited epilepsies are associated with mitochondrial dysfunction, little is known about its role in acquired epilepsies such as TLE. Oxidative stress and mitochondrial dysfunction are emerging as key factors that not only result from epileptic seizures, but may also contribute to epileptogenesis. The occurrence of epilepsy increases with age, and mitochondrial oxidative stress is a leading mechanism of aging and age-related degenerative diseases, suggesting a further involvement of mitochondrial dysfunction in seizure generation. Oxidative damage to one or more cellular targets may indeed affect neuronal excitability and increase seizure susceptibility [5]. The mitochondrion has an essential role in neuronal excitability and neuronal survival. It is a key cellular structure involved in many metabolic functions such as ATP synthesis by oxidative phosphorylation, tricarboxylic acid cycle or fatty acid oxidation. These pathways are fundamental for biological processes such as cell proliferation or death. In the central nervous system, certain mitochondrial dysfunctions have been involved in many neurological diseases and age-related neurodegenerative disorders, including Alzheimer's and Parkinson's diseases [9]. The genetic and biochemical data examined highlight different mechanisms by which mitochondrial bioenergetics is altered in the hereditary defects of complex I [6]. Mitochondrial diseases are frequently caused by a disruption of the respiratory chain. Nevertheless, other mitochondrial functions, including organellar dynamics or metabolite transport, could also be involved in such pathologies [9]. In addition to energy production, mitochondria also play a crucial role in the maintenance of intracellular calcium homeostasis, generation of reactive oxygen species and mechanisms of cell death, but there is a relative paucity of data about the role of mitochondria in epilepsy. Mitochondrial genome analysis is rarely carried out in the investigation of some diseases, among which epilepsy. In mesial temporal lobe epilepsy (MTLE) - hippocampal sclerosis (HS) - cases, mitochondrial genome analysis showed evidence of mitochondrial dysfunctions caused by important mutations associated with epilepsy [7]. Inhibition of *Letm1* and mitochondrial dysfunctions contribute to the development of epileptic seizures in TLE [8]. Early Infantile Epileptic Encephalopathy (EEIE), also known as Ohtahara syndrome, a very severe, intractable and relatively rare pathology, also shows evidence of mitochondrial dysfunctions, i.e. damage to the mitochondrial respiratory chain, and of *SLC25A22* gene mutation in two separate families. These findings suggest that glutamate metabolism should also be considered as an important cause of the Ohtahara syndrome [9].

Mutational analysis of mit-DNA together with clinical and genetic evaluations in a three-generation Chinese Han family has shown the relationship of maternally transmitted mitochondrial mutations with hearing loss and epilepsy [10]. Mutations of mitochondrial carrier genes involved in mitochondrial functions other than oxidative phosphorylation are responsible for carnitine/acylcarnitine carrier deficiency and neonatal myoclonic epilepsy. These disorders are characterized by specific metabolic dysfunctions, depending on the physiological role of the affected carrier in intermediary metabolism. Defects of mitochondrial carriers that

supply mitochondria with the substrates of oxidative phosphorylation, inorganic phosphate and ADP, are responsible for diseases characterized by defective energy production [11].

Besides these studies on mit-DNA mutations, there is evidence of a possible involvement of blood-brain barrier (BBB) in epilepsy. Ultrastructural studies revealed an increase of micropinocytosis in cerebral capillaries during seizures. Studies in the structure of the BBB demonstrated that the capillary basement membrane is thicker in human psychomotor epilepsy [12] and in MTLLE [13]. These studies also suggest that an increase in capillary mitochondria and inter-endothelial tight junctions is possible during seizures. The BBB also regulates nutrient availability to the brain, and under normal conditions excess substrate is made available to the brain for metabolism. Indirect evidence is available to suggest that during seizures, BBB transport may indeed be the rate-limiting step [12]. The unique ultrastructure of brain endothelial cells restricts nonspecific leakage of blood-borne molecules across the BBB. There are findings that during aging gray matter capillaries have thinner walls than white matter capillaries. Thinning is due to loss of pericytes and thinning of the endothelial cytoplasm [14].

Another important study object seemingly not related to the pathogenesis of the epilepsy originating from mitochondrial mutations is the predictability or non-predictability of epileptic seizures. For almost 40 years, neuroscientists thought that epileptic seizures began abruptly, just a few seconds before clinical attacks. But studies and clinical evidence of the last decade demonstrate that attacks develop minutes to hours before clinical onset.

This change in thinking is based on quantitative studies of long digital electroencephalographic (EEG) recordings from patients diagnosed with epilepsy. Evidence that seizures can be predicted is spread over diverse sources in medical, engineering, and patent publications. Techniques used to forecast seizures include frequency-based methods, statistical analysis of EEG signals, non-linear dynamics (deterministic chaos), and intelligent engineered systems [15]. Studying non-linear dynamics in temporal series registered with EEG is accompanied by a wide range of tests and statistical invariants that support the study of deterministic chaos in complex dynamic systems. Throughout the years many non-linear analyses have been conducted on various epilepsy cases. Children with electrical status epilepticus during slow-wave sleep (ESES), for example, show a profound modification of their EEG dynamics with the occurrence, during sleep, of low-dimensional chaotic structure able to modify their brain functioning during sleep [16]. Among the statistical invariants used to evaluate non-linear dynamics of EEG temporal series we have to mention Lyapunov characteristic exponents (LCE) in the reconstructed phase space, Shannon and Kullback-Leibler entropies for the predictability of TLE seizures [17]; the correlation dimension, Kolmogorov-Sinai (KS) entropy (compared to observations on healthy subjects, KS entropy reduces before attacks) [18], as well as other algorithms based on non-linear indices [19-20]. Results agree and are consistent with one another. On evaluating the EEG recording from epileptic children, for example, certain authors [21] show that the phase space, the power spectra, the correlation dimensions and LCE [22] calculated on the base of EEG data reflect the brain's general dynamic characteristics, and can therefore be taken as quantitative indices to evaluate brain health. EEG signals are chaotic non-linear under normal physiological conditions, while signals tend to linear regularity in epilepsy cases. Epileptic seizures can therefore be predicted through the chaotic analysis of EEG signals, such as the entropy level, [23-24] as well as through the fractal analysis of the same EEG data [25-26].

The mitochondrial nature of epileptic diseases and the loss of deterministic chaotic non-linearity in epilepsy are two core aspects of the clinical investigation of Quantum Biophysical Semeiotics [27] and of its bedside diagnosis, which allows to obtain important data for a better comprehension of the pathogenesis of epilepsy, of its genetic predisposition and of its Inherited Real Risk. This will support performing an original pre-primary and primary prevention.

Inherited Real Risk of Epilepsy: physiopathology

The background for all mitochondrial diseases studied by Quantum Biophysical Semeiotics (QBS) is a particular cellular suffering - or functional mitochondrial cytopathy - known as Congenital Acidotic Enzyme-Metabolic Histangiopathy (CAEMH) [28].

If and where the CAEMH is most intensely present, this is a sign of a locally highly altered mit-DNA and consequently of tissue suffering. The result is the formation of one or more QBS constitutions which predispose the organism to some of the most serious degenerative diseases such as type 2 diabetes mellitus, osteoporosis, arteriosclerosis, every form of cancer, solid or liquid, cardiovascular diseases, neurodegenerative diseases etc.

The QBS constitution [29] (whose presence can be diagnosed in every individual since birth by means of a stethoscope) is the initial preclinical stage of a disease which can evolve into an Inherited Real Risk (IRR) of a specific pathology [30]. It indicates that the degenerative preclinical stage (sometimes called for example: pre-diabetes or pre-cancer stage etc.) is dangerously approaching the clinical stage, which is the appearance of the disease itself.

Constitutions do not necessarily evolve into a disease. This is because not all individuals with a pathological constitution develop its corresponding disease in their life. When it does happen, however, the first thing to be examined is the IRR, an indicator of a possible slow and gradual shift to a pathological condition, which is always worsened, but never caused, by its environmental risk factors. IRR diagnosis has therefore a crucial role in QBS, allowing to diagnose the presence of a Real Risk of epilepsy already since birth, and thus confirming the mitochondrial nature of this disease, both if hereditary or acquired, as already pointed out by several authors [2-11].

To understand the pathogenesis of epilepsy - especially at its initial preclinical stage - according to QBS, it is necessary to analyze the data provided by clinical microangiology [31], a QBS branch which studies microcirculation both on the functional and on the structural viewpoint.

Studying microcirculatory dynamics and structures and analyzing the blood flow in arterioles, venules, nutritional capillaries as well as examining the Endo-arteriolar Blocking Devices (EBDs), which are blood regulatory devices, provides important qualitative and quantitative information for a fine and detailed diagnosis. EBDs are tiny contractible and physiologically flexible structures which alternately open and close to regulate blood flow in microcirculation, that is the local flow-motion. There are many types available: EBDs type II are flexible, physiological, ubiquitous and everywhere present in everyone's organism since birth, whereas EBDs type I can either be physiological or pathological. Newly formed pathological EBDs are divided into two subtypes: subtype a) neoplastic; subtype b) aspecific, and they tend to grow in number as the IRR evolves into a disease.

What reveals structural mutation - or microcirculatory remodeling - which grows together with functional mutation, is the presence of EBDs type I. These are anatomically and structurally pathological, stiffer and more obstructing than the physiological ones. Therefore, the opening and closing system of these 'tiny valves' is not flexible, harmonic and contractible as in the physiological one, but stiff and obstructing. This has repercussions on the flow-motion, as can be seen in non-linear dynamics of microcirculatory oscillations, which are physiologically of a deterministic chaotic type, but they lose complexity already in the stage preceding the disease, while gradually tending to linearity when the disease has set in. The deterministic chaotic analysis of EEG signals in patients with epilepsy reveals instead a transition to chaos known as intermittency [32-33], just as epileptic seizures are an intermittent temporary event: stability windows (seizures) in a complex deterministic chaotic order.

QBS deals with the study of microcirculatory deterministic chaotic non-linear oscillations based on fractal dimension calculation [34-36]. This value reduces in case of a pathological IRR (preclinical stage), and the more it reduces, the more the disease approaches a clinical stage (initial stage in chronic evolution). This is confirmed by the progressive reduction in functional and structural complexity which reflects functional mutations (dissociated microcirculatory activation of vasomotility and vasomotion) and structural mutations (presence of local pathological EBDs) in microcirculation.

Structural complexity is geometrically represented by the non-linear dynamic system equilibria observed. This equilibrium physiologically consists of a chaotic attractor (phase space reconstructed equilibrium), which can deteriorate into more simple (low-complexity) orders, such as a periodic equilibrium - limited cycle attractor (pathological IRR) - or a fixed equilibrium (disease at a chronic stage).

In case of an IRR of epilepsy, statistical invariants measuring microcirculatory non-linear dynamics reveal a loss in complexity which shows biological evidence in microcirculatory activity already since birth. This loss is constant in time (not intermittent as in case of EEG signal analysis) and it might slowly reduce in conjunction with a slow progressive degenerative preclinical process (IRR evolution into disease). And after crossing a critical threshold, it could result in an epileptic seizure or an epileptic equivalent.

The measure of deterministic chaos is therefore a useful diagnostic tool both in preclinical stages (microvessels oscillation investigation) and in clinical stages of epilepsy (EEG signal analysis aimed at prediction of epileptic attacks).

Microvessels oscillations are also crucial to investigate the physiopathology of epilepsy and reveal the key role of mit-DNA mutation and of CAEMH in classifying epilepsy as a mitochondrial disease. This is important to define a pre-primary and primary prevention strictly related to its pathogenesis in view of an

improvement in mitochondrial respiration, tissue oxygenation and tissue protection as well as of a retroactive genetic intervention into the altered mitochondrial genome.

Vasomotility is already reduced in case of IRR even though vasomotion is still within physiological values able to compensate for blood outflow. Whenever a difference in the parametric values of vasomotion and vasomotility sets in, the result is an intermediate microcirculatory activation type II, dissociated. In a healthy organism, instead, vasomotion and vasomotility have the same parametric values - microcirculatory activation type I, associated. In other words, microcirculation is where all human tragedies begin and end. The genetically altered mit-DNA causing the above said CAEMH, which in turn can generate one or more QBS constitutions able to evolve - although not necessarily - into pathological IRRs, has always equivalents in the behavior of biologic systems, and in microcirculation in particular. Besides genetic mutation, QBS diagnosis allows to identify specific corresponding local mutations in microcirculatory activity and in its structures (i.e., EBDs, anastomosis (AVA)).

Like all IRRs, the IRR of epilepsy too can undergo many stages with different preclinical variants: from initial stage Real Risk to Real Risk in strong evolution, which is the stage before the formation of the epileptic focus and the appearance of the disease. This progressive degeneration happens simultaneously with and reflects what happens in microcirculation - the number of pathological EBDs increases with time, vasomotility and vasomotion progressively dissociate from each other, although the organism continuously produces new compensatory processes for microcirculatory remodeling. So, while the situation is getting worse and worse in the microworld, nothing yet reveals outside in the macroworld, for example in the blood flow along vessels and arteries. This is the main reason why only the QBS bedside diagnosis is able to objectively verify pre-metabolic syndromes, since it alone is able to quantify microcirculatory dynamics and structures and give them a diagnostic meaning and scope. Pathological EBDs continue to increase in number, vasomotility and vasomotion become more and more different, microcirculatory remodeling is always greater, more continuous and intense, until the organism finally exhausts its compensatory action. This is the point at which the epileptic focus appears and the microworld mutations reveal into the macroworld as matter-energy-information supply (blood flow) to the corresponding parenchyma. At this point the disease sets in and can be clinically diagnosed even with conventional instrumental analyses.

Patients with epilepsy, even those who still don't suffer from seizures, show a limited - generally one alone - brain area where the microcirculatory remodeling takes place, and which is characterized by clear microcirculatory and parenchymal mutations. Only in cases when flow-motion is highly reduced by microvascular structural and functional mutations, which are typical signs of a remodeling event, we can talk about an epileptic focus, worsened but never caused by known environmental risk factors. The main purpose of the well-structured and refined activity of the tissue microvascular unit supported by the normal viscosity of the local interstice is the physiological regulation of blood flow in vessels under 100 micron, whose role is essential in matter-energy-information supply to the corresponding parenchyma.

It is now clear that any mutation in the refined microcirculatory process has serious repercussions on tissue economy, whose pH reduces, while hydrogen ionic H^+ concentration consequently increases, and this is a typical sign of a compromised mitochondrial respiration causing histanic acidosis.

QBS diagnostic approach now allows physicians to identify Constitutions and IRRs since birth, that is to say decades before the possible appearance of the corresponding diseases, and this allows to perform a rational and detailed pre-primary and primary prevention.

Inherited Real Risk of Epilepsy: QBS diagnosis

Traditional physical semeiotics does not allow to diagnose epilepsy neither in patients who do not suffer from seizures nor in seizure-affected individuals if the evaluation is made at a distance from seizures. On the contrary, the Reflex-Diagnostic-Auscultatory Percussion, which is the basis of QBS, allows physicians to diagnose epilepsy and/or the epileptic focus both in individuals who just seem to be healthy because they have no symptoms and in those who suffer from epileptic equivalents which would be hardly identified with a bedside evaluation. In other words, the QBS approach allows to easily recognize an epileptic focus much time before its possible clinical, although atypical, appearance. It follows that QBS has a crucial role in the prevention from epileptic seizures. It has to be noticed, however, that epileptic symptoms and seizures will appear only if the corresponding IRR is particularly serious, i.e. it evolves into an epileptic focus.

To diagnose an IRR of epilepsy, physician should check in sequence the oculo-gastric aspecific reflex, which is asymmetrical, and the cerebro-gastric aspecific reflex in the cerebral hemisphere previously identified, as well as verify whether a microcirculatory activation type I, associated, is present near the epileptic focus. We should also check QBS preconditioning to verify whether the epileptic disease has already set in [27].

Patients with epilepsy have the highest CAEMH value. Besides CAEMH factor, the following reflexes have a crucial role for the diagnosis of epilepsy:

1) Oculo-gastric aspecific reflex:

The latency time (lt) of oculo-gastric aspecific reflex is short, equivalent to 3 seconds (6 seconds in a healthy individual (NN)), and its intensity gets higher than normal, i.e. greater than or equivalent to 2 cm ($NN \leq 1$ cm) when the ocular globe homolateral to epileptic focus is stimulated. The medium to intense pressure over the ocular globe should be exerted in the antero-posterior direction in order to modify the blood vessels behind the eye.

2) Cerebro-gastric aspecific reflex:

Keeping fingers tight together and slightly flexed, physician should apply nails on frontal region skin, first on the right and then on the left, then crawl up until the corresponding midpoint of scalp, proceeding from frontal to occipital region with very slow movements.

When pressure is exerted directly on skin projection of epileptic focus, a cerebro-gastric aspecific reflex is obtained, which can be further increased with light stimulation, apnoea test and forced breathing.

3) Microcirculatory activation type I, associated, near the epileptic focus:

Once the damaged section is identified, generally in the temporo-parietal region, physician should apply a small to medium fingertip pressure on it using the procedure described at point 2): after a 6 second lt, in which an intense ureteral reflex "in toto" (wide interstice) appears, the upper, medium and lower reflexes also follow, oscillating more intensely than in healthy organisms because of an increase of vasomotility and vasomotion values.

Reflex-Diagnostic-Auscultatory Percussion for cerebral diseases, based on the ancient Auscultatory Percussion technique [37], is not only useful for epilepsy, but also for the most frequent and serious pathological processes originating from the central nervous system: cerebral cysts, cancer, acute and chronic ischemia, senile cerebral involution, headache, pituitary gland disease, Alzheimer's disease, Parkinson's disease, ALS and even rare diseases such as Friedreich's ataxia.

Inherited Real Risk of Epilepsy: pre-primary and primary prevention

QBS approach is not only diagnostically relevant, but also useful for an adequate therapeutic monitoring, so as to verify effectiveness of treatments that can be suggested for an appropriate pre-primary and primary therapeutical prevention (according to Manuel's story [38]).

There is a category of 'green therapy' treatments that, if adequately combined and integrated, should allow to make a pathological IRR, like the IRR of epilepsy, a residual factor [39-51]. To make a risk residual does not mean to remove it completely, but to reduce it to a minimum, i.e. to prevent it from growing and evolving into a disease. This category includes: modified Mediterranean diet combined with a daily healthy physical activity, histangic protectors (eg. conjugated melatonin according to Di Bella – Ferrari), substances to improve tissue and mitochondrial oxygenation, coenzyme Q10, vitamins (eg. vitamin C, orange squeezed juices with the addition of 5 lemon drops), ascorbates (eg. potassium ascorbate, sodium ascorbate).

The latest frontier discovered by QBS for pre-primary and primary prevention is a category of treatments known as 'blue therapy' [52] which can heal CAEMH, constitutions and IRRs completely if the corresponding diseases have not set in yet. This strengthens and confirms the existing theories on wave genomics (according to Peter Gariaev) and on genetic/genomic reversibility of nuclear and mitochondrial DNA, and especially the principle of Recursive Genome Function introduced by the American cross-disciplinary scientist and technologist Andras Pellionisz [53]. Clinical and experimental evidence of success in healing many pathological IRRs, among which the IRR of epilepsy, comes from the application of millimeter waves in 'body resonance recording' mode (Cem-Tech, now Ak-Tom) [40], from quantum therapy with sodium bicarbonate [54] (taking advantage of the extraordinary possibilities provided by quantum medicine combined with frequential information acquired by ad hoc substances, where water acts in harmony with the principle of water information memory), and from sulfurous water drinking [55] (eg. Porretta Terme thermal water).

Conclusion

The most recent studies on the pathogenesis of epilepsy related to maternally inherited mitochondrial DNA genetic mutations confirm the previous clinical and experimental evidence of Quantum Biophysical Semeiotics, which is not only able to diagnose epilepsy bedside when the disease has set in, but also to

evaluate its Inherited Real Risk already since birth and before its clinical manifestation, thus allowing to perform an efficient pre-primary and primary prevention.

Acknowledgments

We would like to express our gratitude to Ms Mara Germano, whose English language expertise, added considerably support to this work.

References

- [1] Schmiedel J, Jackson S, Schäfer J, Reichmann H. Mitochondrial cytopathies. *J Neurol.* 2003 Mar;250(3):267-77.
- [2] Baron M, Kudin AP, Kunz WS. Mitochondrial dysfunction in neurodegenerative disorders. *Biochem Soc Trans.* 2007 Nov;35(Pt 5):1228-31.
- [3] Graeber MB, Müller U. Recent developments in the molecular genetics of mitochondrial disorders. *J Neurol Sci.* 1998 Jan 8;153(2):251-63.
- [4] Kang HC, Lee YM, Kim HD. Mitochondrial disease and epilepsy. *Brain Dev.* 2013 Sep;35(8):757-61.
- [5] Waldbaum S, Patel M. Mitochondria, oxidative stress, and temporal lobe epilepsy. *Epilepsy Res.* 2010 Jan;88(1):23-45.
- [6] Papa S, Petruzzella V, Scacco S, Sardanelli AM, Iuso A, Panelli D et al. Pathogenetic mechanisms in hereditary dysfunctions of complex I of the respiratory chain in neurological diseases. *Biochim Biophys Acta.* 2009 May;1787(5):502-17.
- [7] Gurses C, Azakli H, Alptekin A, Cakiris A, Abaci N, Arikan M, et al. Mitochondrial DNA profiling via genomic analysis in mesial temporal lobe epilepsy patients with hippocampal sclerosis. *Gene.* 2014 Apr 1;538(2):323-7.
- [8] Zhang X, Chen G, Lu Y, Liu J, Fang M, Luo J, et al. Association of Mitochondrial Letm1 with Epileptic Seizures. *Cereb Cortex.* 2013 May 3.
- [9] Molinari F. Mitochondria and neonatal epileptic encephalopathies with suppression burst. *J Bioenerg Biomembr.* 2010 Dec;42(6):467-71.
- [10] Zhao JY, Tang XW, Lan JS, Lv JX, Yang L, Li ZY, et al. Hearing loss and epilepsy may be associated with the novel mitochondrial tRNASer(UCN) 7472delC mutation in a Chinese family. *Yi Chuan.* 2008 Dec;30(12):1557-62.
- [11] Palmieri F. Diseases caused by defects of mitochondrial carriers: a review. *Biochim Biophys Acta.* 2008 Jul-Aug;1777(7-8):564-78.
- [12] Cornford EM, Oldendorf WH. Epilepsy and the blood-brain barrier. *Adv Neurol.* 1986;44:787-812.
- [13] Paley EL, Perry G, Sokolova O. Tryptamine induces axonopathy and mitochondriopathy mimicking neurodegenerative diseases via tryptophanyl-tRNA deficiency. *Curr Alzheimer Res.* 2013 Nov;10(9):987-1004.
- [14] Stewart PA, Magliocco M, Hayakawa K, Farrell CL, Del Maestro RF, Girvin J, et al. A quantitative analysis of blood-brain barrier ultrastructure in the aging human. *Microvasc Res.* 1987 Mar;33(2):270-82.
- [15] Litt B, Echaz J. Prediction of epileptic seizures. *Lancet Neurol.* 2002 May;1(1):22-30.
- [16] Ferri R, Elia M, Musumeci SA, Stam CJ. Non-linear EEG analysis in children with epilepsy and electrical status epilepticus during slow-wave sleep (ESES). *Clin Neurophysiol.* 2001 Dec;112(12):2274-80.
- [17] Sabesan S, Narayanan K, Prasad A, Spanias A, Sackellares JC, Iasemidis LD. Predictability of epileptic seizures: a comparative study using Lyapunov exponent and entropy based measures. *Biomed Sci Instrum.* 2003;39:129-35.
- [18] Yambe T, Asano E, Mauyama S, Shiraishi Y, Shibata M, Sekine K, et al. Chaos analysis of electroencephalography and control of seizure attack of epilepsy patients. *Biomed Pharmacother.* 2005 Oct;59 Suppl 1:S236-8.
- [19] Chaovalitwongse W, Iasemidis LD, Pardalos PM, Carney PR, Shiau DS, Sackellares JC. Performance of a seizure warning algorithm based on the dynamics of intracranial EEG. *Epilepsy Res.* 2005 May;64(3):93-113.
- [20] Zhu G, Li Y, Wen PP. Epileptic seizure detection in EEGs signals using a fast weighted horizontal visibility algorithm. *Comput Methods Programs Biomed.* 2014 Jul;115(2):64-75.
- [21] Wang X, Meng J, Qiu T. Research on chaotic behavior of epilepsy electroencephalogram of children based on independent component analysis algorithm. *Sheng Wu Yi Xue Gong Cheng Xue Za Zhi.* 2007 Aug;24(4):835-41.
- [22] Good LB, Sabesan S, Marsh ST, Tsakalis K, Treiman DM, Iasemidis LD. Nonlinear dynamics of seizure prediction in a rodent model of epilepsy. *Nonlinear Dynamics Psychol Life Sci.* 2010 Oct;14(4):411-34.
- [23] Rosso OA. Entropy changes in brain function. *Int J Psychophysiol.* 2007 Apr;64(1):75-80.
- [24] Raiesdana S, Hashemi Golpayegani MR, Nasrabadi AM. Complexity evolution in epileptic seizure. *Conf Proc IEEE Eng Med Biol Soc.* 2008;2008:4110-3.
- [25] Korsakova EA, Khorschhev SK, Barantsevich ER, Slezin VB. Diagnosis of different stages of epileptogenesis by fractal EEG analysis. *Zh Nevrol Psikhiatr Im S S Korsakova.* 2011;111(5):37-41.
- [26] Gao J, Hu J, Tung WW. Facilitating joint chaos and fractal analysis of biosignals through nonlinear adaptive filtering. *PLoS One.* 2011;6(9):e24331.
- [27] Stagnaro S, Marina Neri Stagnaro M. Introduzione alla Semeiotica Biofisica. Il Terreno Oncologico. Ed. Travel Factory, Roma, 2004; pg. 194-195.
- [28] Stagnaro S., Istangiopatia Congenita Acidotica Enzimo-Metabolica. Una Patologia Mitocondriale Ignorata. *Gazz Med. It. – Arch. Sci. Med.* 144, 423, 1985.

- [29] Stagnaro S. Le Costituzioni Semeiotico Biofisiche. Ed. Travel Factory, Roma, 2004.
- [30] Stagnaro S. Reale Rischio Semeiotico Biofisico - Ed. Travel Factory, Roma, 2009.
- [31] Stagnaro S. Introduzione alla Microangiologia Clinica, JOQBS, 2011. Disponibile al link: http://www.sisbq.org/uploads/5/6/8/7/5687930/mc_intro.pdf
- [32] Sitnikova E, Hramov AE, Grubov VV, Ovchinnikov AA, Koronovsky AA. On-off intermittency of thalamo-cortical oscillations in the electroencephalogram of rats with genetic predisposition to absence epilepsy. *Brain Res* 2012, 1436:147-156.
- [33] Goodfellow M, Glendinning P. Mechanisms of Intermittent State Transitions in a Coupled Heterogeneous Oscillator Model of Epilepsy. *The Journal of Mathematical Neuroscience* 2013, 3:17.
- [34] Stagnaro-Neri M, Moscatelli G, Stagnaro S. Biophysical Semeiotics: deterministic Chaos and biological Systems. *Gazz. Med. It. Arch. Sc. Med.* 155, 125, 1996.
- [35] Stagnaro-Neri M, Stagnaro S. Deterministic Chaos, Preconditioning and Myocardial Oxygenation evaluated clinically with the aid of Biophysical Semeiotics in the Diagnosis of ischaemic Heart Disease even silent. *Acta Med. Medit.* 13, 109, 1997.
- [36] Stagnaro-Neri M, Stagnaro S. Deterministic chaotic biological system: the microcirculatory bed. Theoretical and practical aspects. *Gazz. Med. It. – Arch. Sc. Med.* 153, 99, 1994.
- [37] Caramel S. Auscultatory Percussion of the Stomach, according to Sergio Stagnaro. Handbook. QBS press, Lancenigo, Italy, 2014. http://www.sisbq.org/uploads/5/6/8/7/5687930/cardiogarap_handbook.pdf
- [38] Caramel S. La Manuel's story. QBS Magazine, 2011. <http://www.sisbq.org/manuel-story.html>
- [39] Stagnaro S. La Melatonina nella prevenzione primaria dei tumori. Ed. Travel Factory, Roma, 2004.
- [40] Caramel S, Stagnaro S, Pyatakovich FA, Yakunchenko TI, Moryleva ON. Background Millimeter Radiation Influence in Cardiology on patients with metabolic and pre-metabolic syndrome. *Journal of Infrared and Millimeter Waves*, Shanghai, China, Vol.1, February 2014.
- [41] Stagnaro S, Caramel S. A New Way of Therapy based on Water Memory-Information: the Quantum Biophysical Approach. JOQBS, 2011. Disponibile al link: <http://www.sisbq.org/uploads/5/6/8/7/5687930/qbtherapy.pdf>
- [42] Marchionni M, Stagnaro S, Caramel S. The role of 'Modified Mediterranean Diet' and quantum therapy in Alzheimer's disease primary prevention. *JNHA, Springer*, Vol. 18, 1, 2014. [Pub-Med indexed for Medline]
- [43] Stagnaro S, Caramel S. Inherited Real Risk of Coronary Artery Disease: pathophysiology, diagnosis and primary prevention. *Epidemiology and Cardiovascular Prevention. Brief Communication.* 8th International Congress of Cardiology in the internet. Published: 28 October 2013. FAC Federaciòn Argentina de Cardiologia Disponibile al link: http://fac.org.ar/8cvc/llave/tl054_stagnaro/tl054_stagnaro.php
- [44] Stagnaro S, Caramel S. The Inherited Real Risk of Coronary Artery Disease, *Nature PG., EJCN, European Journal Clinical Nutrition, Nature PG*, 2013 Apr 24. [Pub-Med indexed for Medline]
- [45] Marchionni M, Caramel S, Stagnaro S. Inherited real risk of Alzheimer's disease: bedside diagnosis and primary prevention. *Front Aging Neuroscience*, 2013. [Pub-Med indexed for Medline] http://www.frontiersin.org/Aging_Neuroscience/10.3389/fnagi.2013.00013/full
- [46] Marchionni M, Caramel S, Stagnaro S. Quantum Biophysical Semeiotics Bedside Diagnosing Inherited Real Risk of Brain Disorders: Boezio's Sign. *Neurodegenerative Disease Primary Prevention.* JOQBS, 2013. http://www.sisbq.org/uploads/5/6/8/7/5687930/boeziosign_2013.pdf
- [47] Stagnaro S, Caramel S. Inherited Real Risk of Type 2 Diabetes Mellitus: bedside diagnosis, pathophysiology and primary prevention. *Front Endocrinol (Lausanne)*, 2013. [Pub-Med indexed for Medline] <http://www.frontiersin.org/Diabetes/10.3389/fendo.2013.00017/full>
- [48] Stagnaro S, Caramel S. The Role of Modified Mediterranean Diet and Quantum Therapy in Oncological Primary Prevention. *Bentham PG., Current Nutrition & Food Science*, 2013. 2212-3881.9: 1. <http://eurekaselect.com/106105/article>
- [49] Stagnaro S, Caramel S. The Role of Modified Mediterranean Diet and Quantum Therapy in Type 2 Diabetes Mellitus Primary Prevention. *LifeScienceGlobal.* February 2013, *Journal of Pharmacy and Nutrition Sciences*, 2013, 3.
- [50] Stagnaro S, Caramel S. Quantum Therapy: A New Way in Osteoporosis Primary Prevention and Treatment. *Journal of Pharmacy and Nutrition Sciences*, February 2012.
- [51] Stagnaro S, Caramel S. The Role of Mediterranean Diet, CoQ10 and Conjugated-Melatonin in Osteoporosis Primary Prevention and Therapy *Current Nutrition & Food Bentham Science Volume 8, Number 1, February 2012* Pp.55-62.
- [52] Stagnaro S. Il Manifesto della Medicina Semeiotico Biofisico Quantistica Ristrutturante (MSBQR), JOQBS, 2013. Disponibile al link: <http://www.sisbq.org/uploads/5/6/8/7/5687930/manifestomedicinasbqristrutturante2013.pdf>
- [53] Stagnaro S, Caramel S. The Principle of Recursive Genome Function: QBS clinical and experimental evidences. JOQBS, 2011. Disponibile al link: http://www.sisbq.org/uploads/5/6/8/7/5687930/prgf_qbsevidences.pdf
- [54] Stagnaro S. Il Reale Rischio Congenito epilettico. www.sisbq.org. 2014. Disponibile al link: http://www.sisbq.org/uploads/5/6/8/7/5687930/rrc_epilessia.pdf
- [55] Caramel S. Meccanismi d'Azione Sconosciuti dell'Acqua Termale Sulfurea. JOQBS, 2012. Available at link: <http://www.sisbq.org/uploads/5/6/8/7/5687930/h2s.pdf>