

"Quantum Biophysical Semeiotics Bedside Diagnosing Inherited Real Risk of Brain Disorders: Boezio's Sign". Neurodegenerative Disease Primary Prevention.

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Abstract

This is an overview of 'Quantum Biophysical Semeiotics' (QBS) signs for the diagnosis of neurodegenerative disorders, even potential or initial and symptomless, such as Alzheimer's Disease (AD), Parkinson's Disease (PD), Senile Dementia (SD), Multiple Sclerosis (MS), Amyotrophic Lateral Sclerosis (ALS), Niemann-Pick Type ABC Disease (NPD).

This article highlights the aspecific sign termed 'Inherited Real Risk' of brain disorder, which provides useful information regarding differential diagnosis between brain cancer and other cerebral diseases, both in clinical and pre-clinical stages. The 'Inherited Real Risk' of brain disorder need then to be integrated with other specific signs, according to different trigger-points related to different cerebral disorders: in this paper, Boezio's sign is illustrated in order to verify if in a given patient the congenital risk of Amyotrophic Lateral Sclerosis (ALS) is real. In addition to that, taking into account the recursive genetic effects underlying neurodegenerative pathologies, an early QBS diagnosis allows a primary and pre-primary prevention, of such ominous diseases.

QBS is an extension of medical semeiotics. It is grounded on a multidisciplinary approach that involves chemistry and biology, genetics and neuroscience, chaos theory and quantum physics. It is based on the method of 'Auscultatory Percussion', through which by means of the common stethoscope, it is possible to listen to the signs that the body gives us when appropriately stimulated. The stimuli are used to induce auscultatory percussion reflexes in precise and well defined biological systems of the human body, thus giving local qualitative information on their physiological and pathological condition, no matter whether potential, actively developing but still clinically silent (that is not yet evident through usual clinical, laboratory and radiological investigations) or in acute or chronic phases.

1. State of Art

Amyotrophic Lateral Sclerosis (ALS) is the third most common human late-adult-onset progressive neurodegenerative disorder of the voluntary motor system, affecting motor neurons [1, 8, 12]. This is a multifactorial and multisystem disease with a *really* complex pathogenesis [16].

Selective vulnerability of motor neurons likely arises from a combination of several mechanisms, including protein misfolding, mitochondrial dysfunction, oxidative damage, defective axonal transport of mitochondria along microtubules [4], glutamate excitotoxicity, accumulation of intracellular aggregates, glia cell pathology, growth factor deficiency, aberrant RNA metabolism and inflammation [11, 13].

In primary mitochondrial and neurodegenerative disorders, there is strong evidence that mitochondrial dysfunction occurs early and it is likely to be a converging point of multiple pathways underlying the ALS pathogenesis and progression, as confirmed by several lines of evidences [3, 4, 5, 6, 10, 14]. Mitochondria play a central role in ATP supply to cells through oxidative phosphorylation (OXPHOS), synthesis of key molecules and response to oxidative stress, as well as in apoptosis. Each of these factors could also be associated with essential mechanisms involved in neurodegenerative diseases. Recent studies revealed that changes in mitochondria membrane fluidity might have a direct impact on membrane-based processes such as fission-associated morphogenic changes, opening of the mitochondrial permeability transition pore or oxidative phosphorylation at the complexes of the electron transport chain [6, 7, 9]. There are evidences that Complex I deficiency and both reduction in intracellular ATP and increase in intracellular ADP content may be involved in the progression and pathogenesis of ALS [6].

Mitochondria contain many redox enzymes and naturally occurring impairment of oxidative phosphorylation at the level of mitochondrial respiratory chain generate reactive oxygen species (ROS). Mutations in mitochondrial DNA (mit-DNA), generation and presence of ROS and environmental factors may contribute to energy failure and lead to neurodegenerative diseases [5]; mitochondrial respiratory chain failure is the leading cause of death in patients involved by amyotrophic lateral sclerosis (ALS) [2]. Previous findings have suggested a specific impairment of mitochondrial function in skeletal muscle of at least a limited number of patients and an oxygen radical-induced impairment of mit-DNA is of pathophysiological significance in the etiology of at least a subgroup of patients with SALS (Sporadic ALS) [11].

Furthermore, brain mitochondrial dysfunction is closely linked to the physiology and pathophysiology of endothelial cells and the functioning of their mitochondria. Endothelial dysfunction has been implicated as a crucial event in the development of several CNS disorders, such as Alzheimer disease, Parkinson disease, ALS. Breakdown of the blood-brain barrier (BBB) as a result of disruption of tight junctions and transporters, leads to increased leukocyte transmigration and is an early event in the pathology of these disorders. BBB breakdown thus leads to neuro-inflammation and oxidative stress, which are implicated in the pathogenesis of CNS disease [15].

The impact of BBB and blood-spinal cord barriers (BSCB) damage and their impairment in ALS pathogenesis and microvascular pathology is a novel promising research topic [16, 17]. BBB is essential for the maintenance and regulation of the neural microenvironment [19]. Compelling evidence of impairment of all neurovascular unit components including the analysis of the normal and impaired BBB/BSCB in both patients and animal models, lead to classification of ALS as a neurovascular disease [16]: a hemodynamic mechanism may cause this neurodegenerative disease [18], because there are evidences of abnormal blood flow, that may explain the BSCB damage in ALS.

All these promising researches, however, appear fragmented, as many small pieces of a big puzzle still to assemble and unite in a unified framework. Quantum Biophysical Semeiotics (QBS) [20] offers an approach 'as a whole' of the patho-physiology of inherited mitochondrial neurodegenerative diseases.

Functional and structural impairments in the 'macro-world' (veins, arteries, hemodynamic, newborn-pathological Endoarteriolar Blocking Devices obstructing blood flow) observed in the above-mentioned studies are related to the current disease. According to QBS, most of these impairments are inherited through the mothers and already present, in a similar form, in micro-vascular neurobiological systems and clinically observable.

In the frame of QBS theory, the combination of Clinical Microangiopathy¹ [21, 22] and 'Angiobiopathy' theory² [23], allows to merge the hypothesis of ALS as neurological microvascular - based

disease and the researches focused on mitochondrial dysfunction according to the inherited genetic causes of this neurodegenerative pathology, i.e., the congenital alteration of mit-DNA in related neuronal cells.

QBS is a new discipline in medical field and an extension of the classical semeiotics with the support of quantum and complexity theories. It is a scientific trans-disciplinary approach that is based on the 'Congenital Acidotic Enzyme-Metabolic Histangiopathy' (CAEMH) [24], a unique mitochondrial cytopathy that is present at birth and subject to medical therapy.

The presence of intense CAEMH in a well-defined area (i.e., myocardium) is due to gene mutations in both n-DNA and mit-DNA. This is the basis for one or more QBS constitutions which could bring about their respective Inherited Real Risks (IRR). IRR are characterized by localized microcirculatory remodeling, especially intense under environmental risk factors, showing typical type I, subtype a) Oncological and/or b) aspecific, 'Endoarteriolar Blocking Devices' (EBD), one of the authors discovered and illustrated previously [25].

The theoretical basis and methodology of QBS can be implemented in a number of practical bedside tests (performed using a stethoscope through viscera's auscultatory percussion) the aim of which is that of assessing levels of function of mitochondria in different biological systems (i.e., stomach, ureter etc.). Thanks to this practical methodology, even from birth the presence of the IRR of many diseases linked with 'QBS Constitutions' [26], can be clinically demonstrated and, following this QBS-based semeiotic diagnostic process, an intelligent prevention strategy can be implemented only on those at real risk (with IRR of any disease).

The QBS method allows the clinical and pre-clinical³ diagnosis of the most severe diseases as, for example, solid and liquid forms of cancer, Type II Diabetes Mellitus and coronary heart diseases, as well as the IRR of brain disorder (illustrated in the next chapter) [27, 28]; this is achieved also through the auscultatory percussion of the stomach [29 - 31].

This gastric diagnosis is consistent and dually reflects the informative nature and quality of parameters collected by QBS microcirculatory investigations that are in accord with 'Clinical Microangiology'. The patho-physiology of QBS reflexes is based upon local microvascular conditions. In case of genetic alteration of both DNAs, there is a microcirculatory remodelling due to vasomotility and vasomotion impairment (e.g., functional imperfection) and structural obstructions, i.e., pathological EBD and Arteriovenous Anastomosis (AVA).

In this paper we introduce the QBS diagnosis of some IRR of brain disorders, i.e., Parkinson's disease, Multiple Sclerosis and Senile Dementia, and we deepen the clinical and pre-clinical assessment of Inherited Real Risk of Amyotrophic Lateral Sclerosis – ALS.

2. The 'Inherited Real Risk' of brain disorders (aspecific sign)

Within the several QBS signs, those offered by Auscultatory Percussion of the Stomach are easier to understand and to apply in the daily practice. One of these is the simultaneous cerebral-gastric aspecific reflex in case of "intense" digital pressure on brain's trigger points. This reflex is related with the non-local quantum behavior of biological systems [32 - 34].

In health, "intense" digital pressure on brain's trigger points (any point of the cranium), does not provoke simultaneously gastric aspecific reflex (the reflex appears just after 16 seconds due to physiological tissue acidosis), thus there is not IRR of brain disorders (negative Marchionni's sign): this is the physiological state [35].

Under the above mentioned conditions, if the stomach simultaneously dilates, increasing its size less than 1 cm (about 0.5 cm), then this represents a QBS sign of positive CAEMH (98% of subjects have got positive CAEMH).

If the stomach moves simultaneously, dilating for at least 1 cm or more, then there is IRR of brain disorders or overt brain disease (if the stomach dilates more than 1.5 cm): positive Marchionni's sign (Table 1). This is an aspecific sign, but it becomes specific⁴ if the microcirculatory remodeling [36-38] is present in the typical areas of the related cerebral disorder (Table 2).

If the stomach increases its size simultaneously, dilating for at least 1 cm, and then it contracts, then there is IRR of brain cancer or overt cerebral cancer (if the stomach dilates more than 1.5 cm and then contracts).

Latency time (Lt)	tonic Gastric Contraction (tGC)	Intensity	Diagnosis
Lt = 16 seconds	No		Health
Lt = 0 seconds – the stomach dilates “simultaneously”	No	Intensity ~ 0.5 cm	CAEMH
Lt = 0 seconds - the stomach dilates “simultaneously”	No	Intensity ≥ 1 cm	IRR of Brain Disorder (positive Marchionni’s sign)
Lt = 0 seconds - the stomach dilates simultaneously	No	Intensity ≥ 1.5 cm	Overt Brain Disorder
Lt = 0 seconds - the stomach dilates “simultaneously”	Yes – after dilation the stomach contracts	Intensity ≥ 1 cm	IRR of Brain Cancer
Lt = 0 seconds - the stomach dilates “simultaneously”	Yes - after dilation the stomach contracts	Intensity ≥ 1.5 cm	Overt Brain Cancer

Table 1. Cerebral-Gastric Aspecific Reflex under “intense” digital pressure on brain’s trigger points

3. Inherited Real Risk of brain disorders (specific sign)

If there is a IRR of brain disorders (which is an aspecific sign), in order to discover of which kind of cerebral disease an individual is at risk, the doctors must refine the diagnosis making an investigation more focused on the correct localization of the underlying clinical neurological disorder. This is achieved through QBS assessment of the related specific signs.

In Table 2 the trigger points related to some cerebral disorders, i.e., Alzheimer’s Disease (AD)[39], Parkinson’s Disease (PD), Senile Dementia (SD), Multiple Sclerosis (MS), Amyotrophic Lateral Sclerosis (ALS), Niemann-Pick Type A,B,C (1 and 2) Disease (NPD), are evidenced. Trigger points stand for the points of digital pressure to perform the QBS diagnosis, i.e., through Auscultatory Percussion of the Stomach.

Inherited Real Risk of Brain Disorder (specific sign)	Trigger Points
Alzheimer’s Disease (AD)	Pre-Frontal, Frontal Area, Motor Area (Brodmann Area 4, gyrus precentralis) , Temporal Area (temporal gyri, superior, middle and inferior)
Parkinson’s Disease (PD)	Pre-Frontal, Frontal Area, Motor Area (Brodmann Area 4, gyrus precentralis)
Senile Dementia (SD)	Motor Area (Brodmann Area 4, gyrus precentralis) , Temporal Area (temporal gyri, superior, middle and inferior).
Multiple Sclerosis (MS)	Pre-Frontal, Frontal Area, Occipital Area, Motor Area (Brodmann Area 4, gyrus precentralis) , Temporal Area (temporal gyri, superior, middle and inferior)
Amyotrophic Lateral Sclerosis (ALS)	Somato-sensorial cortex (Brodmann Areas 3,1,2, gyrus postcentralis)
Niemann-Pick Type A, B, C 1-2 Disease (NPD)	Right and Left Temporal Area (temporal gyri, superior, middle and inferior)

Table 2. IRR of Brain Disorders: trigger points

Niemann-Pick Disease⁵ is firstly revealed by a positive Marchionni Sign (Chapter 2) with a reflex’ intensity of at least 4 cm, never observed in other signs of Brain Disorders [40]. Interestingly, in Niemann-Pick Disease

are present from birth both Antognetti's Sign and Caotino's Sign, which are thus characteristic of such a lisosomal disorder of lipid metabolism, due to heritable impairment of Acid Sphingomyelinase [41, 42].

ADDENDA: In order to approximate the site of the central sulcus (and therefore of the motor area and somato-sensorial parietal areas) the position on the scalp of a number of craniometric and anatomical landmarks must be identified (Table 2 bis).

Inion	The bony prominence just above the torcular of Herophil
Nasion	In the midline, the junction between the frontal and nasal bones
Midline sagittal line of the skull	line connecting the nasion and inion (its 1/2 and 3/4 points are also marked)
Superior rolandic point	on the nasion-to-inion midsagittal line, is located 2 cm posterior to the midpoint.
Inferior rolandic point	It is the crossing point between (1) a line extending from superior rolandic point to the midpoint of the zygomatic arch's superior margin and (2) the sylvian fissure's line
Sylvian fissure's line	A line connecting , on the lateral surface of the scalp, the fronto-zygomatic point with the 3/4 point (on the posterior part of the nasion-inion line)

Table 2 bis. Craniometric and anatomical landmarks

A correct identification of the inferior and superior rolandic points is mandatory in order to localize the central sulcus, which can be approximated by a line connecting the inferior and superior rolandic points.

In some cases, a specific diagnosis of IRR of Brain Disorder can be strengthened with other quantum biophysical semeiotics signs. For example, Parkinson Disease is characterized, from QBS view-point, by a prolonged *Simulated Sucking Test*.

In health, the duration of the test last for 6 seconds, than it lowers to 5 seconds soon thereafter.

In individual with Oncological Terrain test's duration raises to 7 seconds or more, in relation to the seriousness of the predisposition to cancer. The duration of subsequent Gastric Aspecific Reflex increases in a significant manner, i.e., to 8 or more seconds.

In Parkinson Disease, since its initial stages, *Simulated Sucking Test* brings about a characteristic Gastric aspecific reflex longer than 15 seconds, due to increased prolactin [20, 35, 43].

4. Inherited Real Risk of Amyotrophic Lateral Sclerosis

Notoriously, the diagnosis of Amyotrophic Lateral Sclerosis, called also "Lou Gehrig's disease", the most common form of the motor neuron diseases, is generally later, due to the difficulty of clinically recognizing its early symptomatology. Typically only the motor function is affected without significant abnormalities of sensory function or cerebellar or extrapyramidal function. Weight loss (especially at the early stage), muscle cramps and fasciculations are present in association with distal asymmetric localized hypostenia (reduced handgrip, hand clumsiness, footdrop or gait unsteadiness) or symptoms of bulbar dysfunction such as dysphagia or dysarthria.

On examination the clinical findings are indicative of lower motor neuron involvement (hypostenia, hypotrophy or atrophy, fasciculations) and/or upper motor neuron involvement (hyperreflexia, muscular hypertone or spasticity); Babinski and Hoffmann signs may be present as well. In localized regions of muscular hypotrophy or atrophy, the presence of hyperreflexia or spasticity, not associated with hypoesthesia, is a peculiar finding very typical of ALS.

The diagnosis of ALS is clinical and relies upon the presence of positive findings (UMN and LMN signs, as well as progression of the symptomatology), negative findings (absence of abnormalities affecting the

sensory function, visual or sphincter impairment, AD, extrapyramidal signs or symptoms, exclusion of other medical disorder which may mimic ALS) and supportive findings.

In this respect, EMG and NCS are most useful in order to detect findings related to denervation (truncal, bulbar or monomelic) or diffuse chronic or acute lower motor neurons axonal loss not yet evident/apparent during the clinical examination. No pathognomonic serum or CSF biochemical marker is available in order to confirm the clinical diagnosis.

A correct diagnosis at the earliest stage when the extension of signs or symptoms is limited may be very difficult and it is estimated that 13-18 months is the mean time which intercur from the onset of clinical signs and symptoms and a confirmed diagnosis of ALS. Importantly, there is not nowadays efficacious therapy of ALS.

Despite the current lack of an exact knowledge regarding the multiple causal pathological factors and their interactions at different level of time and space (i.e., physical, chemical and biological compartments) leading to ALS (and this also applies also to many other cerebral diseases), this ominous neurological disorder can involve exclusively individuals with IRR of Brain Disorder which proves to be specific in relation to its location in the brain, as one of the Authors has illustrated in former papers [35].

We now describe a precious sign, Boezio's Sign, which plays a central role in clinical diagnosis of IRR of ALS, since it can be assessed and demonstrated even in the newborn having an IRR of ALS.

In health, an "intense" leg skin stimulation by mean of a pinching, simultaneously brings about, at the level of the controlateral somato-sensorial parietal cortex, a microcirculatory activation type I, associated, followed suddenly by identical activation of omolateral motor area: these modifications can be detected with QBS [20, 29-31], as well as with PET and SPECT. This simultaneous activation is due to no-local realm in biological systems [32-33].

On the contrary, in individual involved by IRR of ALS, and clearly by overt ALS, under the experimental condition, illustrated above, brain microcirculatory activation occurs after a latency time, whose length is directly related to the seriousness of the underlying disorder: 2-4 seconds in presence of IRR of ALS and 5 seconds or more in overt ALS (Table 4).

a) Diagnosis of Inherited Real Risk of ALS (Boezio's Sign)

If there is the 'Inherited Real Risk' of Brain Disorder (positive Marchionni's sign) which is an aspecific semeiotic sign, we should refine the QBS diagnosis in order to understand what kind of brain disorder is at risk, i.e., if there is the 'Inherited Real Risk' of AD, PD, MS, DS, ALS, etc (specific signs). In this paper we refine the diagnosis of 'Inherited Real Risk' of Amyotrophic Lateral Sclerosis (ALS). In this respect the 'Cerebral Gastric Aspecific Reflex', evoked under "light-mean" stimulation with digital pressure upon the cerebral trigger points related to the investigated risks of disorder, i.e., ALS, plays a key role. In Table 3, the ALS 'Cerebral Gastric Aspecific Reflex' (ALS Ce.G.A.R.), under "light-moderate" digital pressure on any point of the skin projection of the controlateral somato-sensorial parietal cortex (Figure 1) and "intense" pinching stimulation of any point of contro-lateral leg skin, is shown.

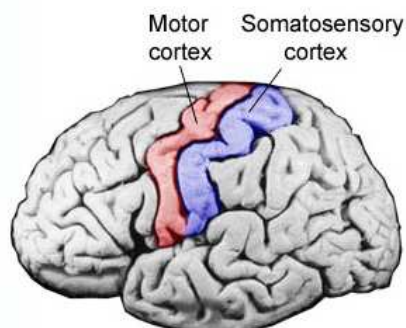


Figure 1

In health, the 'Latency time' of ALS Ce.G.A.R. is of 8 seconds while, in presence of 'Inherited Real Risk' of ALS in evolution, the Lt is less than 8 seconds.

In the beginning stages of ALS IRR Lt is still 8 seconds in the first QBS diagnosis (the same of physiological latency time), but reflex duration is 4 seconds or more ($NN > 3sec. < 4 sec.$). This fact induce to repeat again the diagnostic QBS test after exactly a 5 seconds pause from the first diagnosis ("Brain

Preconditioning"): the Lt is less than 16 sec in patients with ALS IRR (positive Boezio's sign), while in health we observe exactly the double value.

Latency time (Lt) in seconds	Latency time after a pause of 5 sec. : (brain preconditioning)	Duration (in seconds)	Diagnosis
Lt = 8	Lt = 16	$3 < D < 4$	Health (negative Boezio's sign) – if Marchionni sign is positive, it needs to investigate other specific signs
Lt = 8	Lt < 16	$D \geq 4$	ALS Inherited Real Risk (positive Boezio's Sign)
$7 < Lt < 8$	$14 < Lt < 16$	$D > 4$	ALS Inherited Real Risk in evolution
$Lt \leq 7$	Lt < 14	$D \gg 4$	Overt ALS

Table 3. ALS - Gastric Aspecific Reflex (G. A. R.)

b) **ALS: microcirculatory dynamics, primary and pre-primary prevention**

Microcirculation (ignoring the many transitional forms) shows three basic types of activation:

- 1) type I, Associated (the term 'associated' means that vasomotility and vasomotion show the same physiological behavior);
- 2) type II intermediate, partially dissociated (pre-metabolic syndrome, dissociated because vasomotility and vasomotion have a different behavior);
- 3) type III completely dissociated (pathological microcirculation, typical of overt disease).

In health, the basal value of microcircle (at rest), i.e., the duration of the first upper ureteral reflex under "light-moderate" digital pressure on ALS trigger points lasts for 6 seconds (diastole), and then a systole (6 seconds) follows, before appearing the second reflex. The period is given by summing diastole and systole, so we observe a period of 12 seconds (Figure 2).

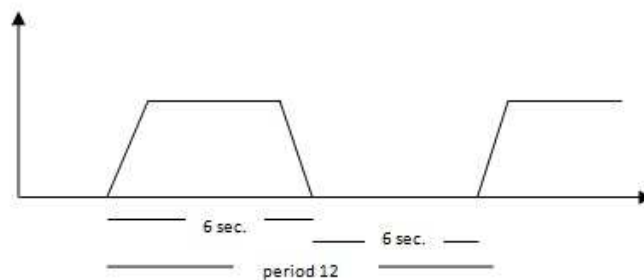


Figure 2

Under "light-moderate" digital pressure on any point of the skin projection of the contralateral somato-sensorial parietal cortex and "intense" pinching stimulation of any point of contro-lateral leg skin,

there is Microcirculatory Activation, type 1, associated: simultaneous reflex (no latency time), diastole 11 seconds and systole 1 second (Figure 3).

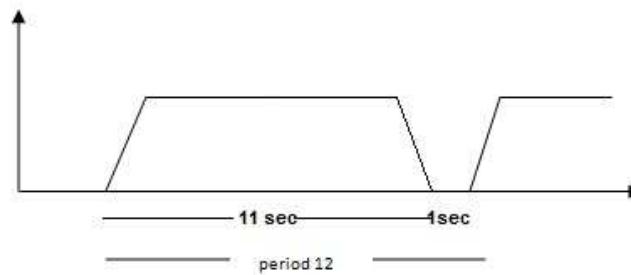


Figure 3

In case of 'Inherited Real Risk' of ALS, there is a functional alteration of microcirculatory dynamics evidenced by an impairment of vasomotility and vasomotion (microcirculatory activation, type 2, dissociated) as well as structural abnormalities such as the presence of pathological Endoarteriolar Blocking Devices - EBD [25].

This is a similar behavior to other inherited real risks of disorders, such as diabetics, rheumatic, gouts one, where the remodeling is characterized by new-formed aspecific pathologic EBD, all equals in term of structure and function, but they turn specific in relation with their tissue location.

These functional and structural abnormalities increase along time, with the evolution of the IRR (pre-clinical stage) to the overt pathology (microcirculatory activation, type 3, dissociated). From the moment of the digital stimulation is important to count the latency time of the reflex: in a physiological diastole there is not any latency time (simultaneous upper ureteral reflex) , while in case of IRR of ALS there is a Lt (latency time) between 2 and 4 seconds, sign of tissue acidosis which increases with the evolution of pre-metabolic syndrome to metabolic syndrome (Lt of 5 seconds or more, depending of the severity of ALS, in case of pathology).

The intensity of the reflex represents the dilation of the viscera: physiologically the uretere's dilates for about 2 cm, while the dilation diminish progressively in case of IRR of ALS or overt ALS, as well as we observe an impairment between dilation of vasomotility and vasomotion.

QBS tools are not only useful for diagnostic purposes, but also for therapeutic advices, because they are able to measure the microcirculatory activity before and after each preventive therapy's treatment, in order to understand the effectiveness of remedies.

Some years ago, one of the author [26] let us an open question: are QBS Constitutions and Inherited Real Risk of degenerative pathologies reversible?

Through a proper prevention treatment termed 'type A' or 'green' therapy a genetic reversibility for future generations is possible [44], but this could not be enough for the current generations, especially under environmental negative conditions.

The green therapy⁶ stimulates the activity of mitochondria by acting on metabolism (chemical processes), peptides' net (electric-electronic processes), but also improving, normalizing mitochondrial and tissue oxygenation, expression of the normal operation of mitochondrial oxidative phosphorylation. Indeed, the mitochondrial functional cytopathy above mentioned (CAEMH) is the *condition sine qua non* of more frequent and severe human disease and not.

By this way tissue oxygenation and mitochondrial activity are improved, mitochondria are running well, but it remains the genetic alteration of mit-DNA: CAEMH, QBS Constitutions and IRR of diseases are still positive, but the Inherited Real Risk of ALS, becomes 'residual'. This means that a continuative 'type A' therapy averts the risk that the disease can emerge, despite the genetic problem is not yet healed.

In fact, under a continuative 'green' therapy the Lt of ALS 'Brain Gastric Aspecific Reflex' under mean digital stimulation of ALS trigger-points rises maximally to 12 seconds, instead of the basal 8 seconds or less (Table 5, 4th column).

A latency time of 12 seconds corresponds to a physiological microcirculatory activation, type 1, associated, diastole 7-9 seconds, systole 5-3 seconds.

	Basal Microcirculatory (i.e., at rest) Slight stimulation of somato-sensorial parietal cortex skin trigger-points.			Microcirculatory Activation, caused by INTENSE stimulation of leg skin		
	Latency/Intensity	diastole	systole	Latency/Intensity	diastole	systole
Health	Lt = 0 sec. (than two small ureteral reflexes occur) Int. = 0.5 – 1.5 cm	6 sec. Vasomotility = vasomotion	6 sec. Vasomotility = vasomotion	Lt = 0 sec. Int. = 2 cm	11 sec. Type 1 A. associated	1 sec. Type 1 A. associated
IRR of ALS	Lt = Ibidem	7 sec. vasomotility 6 sec. vasomotion Type 2 dissociated Activation	5 sec. vasomotility 6 sec. vasomotion Type 2 dissociated Activation	Lt = 2-4 sec. Int. = 1.5 cm vasomotility Int. = 1.5 cm vasomotion	10-9 sec. vasomotility 5 sec. vasomotion Type 2 dissociated Activation	2-1 sec. vasomotility 7 sec. vasomotion Type2 dissociated Activation
Overt ALS	Lt = Ibidem	8 sec. vasomotility 6 sec. vasomotion Type 3 dissociated Activation	4 sec. vasomotility 6 sec. vasomotion Type 3. dissociated Activation	Lt ≥ 5 sec. Int. < 1 cm vasomotility Int. < 0.5 cm vasomotion	8-7 sec. vasomotility 4 sec. vasomotion Type 3 dissociated Activation	4-5 sec. vasomotility 8 sec. vasomotion Type 3 dissociated Activation
ALS IRR after blue therapy (first week)	Lt = Ibidem	11 sec. Vasomotility = vasomotion	1 sec. Vasomotility = vasomotion	Lt → 0 sec. Int. = 2 cm	11 sec. Type 1 A. associated	1 sec. Type 1 A. associated
ALS IRR after blue therapy (from about the first month)	Lt = Ibidem	6.5 sec. Vasomotility = vasomotion	5.5 sec. Vasomotility = vasomotion	Lt = 0 sec. Int. = 2 cm	10 sec. Type 1 A. associated	2 sec. Type 1 A. associated
ALS IRR after blue therapy (after 9 months)	Lt = Ibidem	6 sec. Vasomotility = vasomotion	6 sec. Vasomotility = vasomotion	Lt = 0 sec. Int. = 2 cm	11 sec. Type 1 A. associated	1 sec. Type 1 A. associated

Table 4. ALS microcirculatory activation

One of the authors has recently discover a new class of treatments for preventive purposes termed ‘type B’ or ‘blue’ therapy⁷ [43], in accord with the Principle of Recursive Genome Function (PRGF) by Andras Pellionisz [45 – 49].

Diagnosis	Health	IRR of ALS	Under Green Therapy	During Blue Therapy	After Blue Therapy (about 9 months later)
ALS Brain Gastric Aspecific Reflex - Latency Time	Lt = 8 sec.	Lt ≤ 8 sec.	Lt = 12 sec.	Lt = 16 sec. and then gradually slowly decreases	Lt = 8 sec.

Table 5

‘Type B’ therapy differs from the previous one for the following reasons: the Lt of ALS ‘Brain Gastric Aspecific Reflex’ under mean digital stimulation of ALS trigger-points rises to 16 seconds, doubling the basal

physiological one (Table 5, 5th column), before slowly decreasing to 8 seconds over a period of about 9 months; this gastric parametrical value correspond to a physiological extremely high microcirculatory activation, type 1, associated, maximal value never observed before, diastole 11 seconds, systole 1 seconds (Table 4).

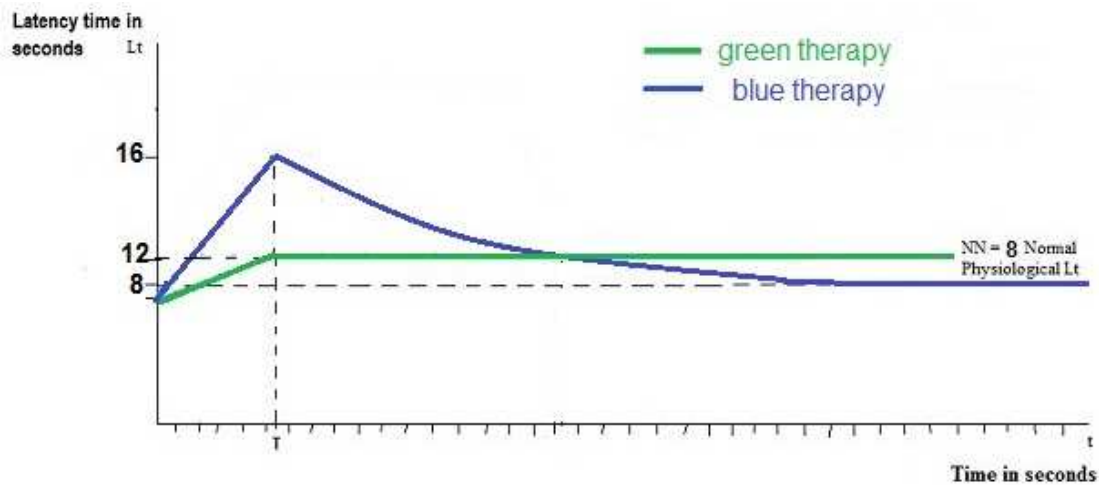


Figure 4

The diagram in Figure 4 shows the differences between “green” and “blue” therapy in terms of latency time of ALS G.A.R. over time. In case of Inherited Real Risk of ALS the latency time of ALS gastric specific reflex is 8 seconds or less ($Lt \leq 8$).

Under a “green” therapy (green line) the Lt rises to 12 seconds, so reducing tissue acidosis. This kind of therapy must be continuative to maintain a sufficient level of mitochondrial and tissue oxygenation and the risk “residual”, otherwise the Lt would decrease restoring the IRR of ALS. The ‘type A’ therapy cures but it does not heal.

Under a “blue” therapy (blue line), administered at the moment T , the Lt of ALS G.A.R. rises to 16 seconds and there is an extremely high microcirculatory activation (arteriolar diastole of contralateral sensory somatic area is 11 seconds, arteriolar systole 1 seconds, followed after 2 seconds by the same activation of ipsilateral motor area) as in Figure 3. QBS diagnosis ascertains the healing of CAEMH after 5 minutes and of IRR of ALS after 10 minutes from the beginning of the application. From the moment T , an intense DNA’s reprogramming and genome’s restructuring activity starts up and lasts for about 9 months. During this period of genetic restructuring and normalization, QBS monitoring states that Lt of ALS G.A.R. gradually decreases till the basal physiological value of 8 seconds, i.e., the high microcirculatory activity diminishes after about one month, but it remains slightly activated till the end of the ninth month, a period of plausible normalization of the genetic restructuring just completed, before ceasing and stabilizing at rest (Table 4, last row, diastole 6 seconds, systole 6 seconds). The ‘type B’ preventive therapy heals the IRR of ALS, as confirmed by the first case of IRR of ALS healed last August 6th, 2012 by one of the authors.

After about 9 months from the moment T , ‘blue’ therapy’s effects are over (ALS G.A.R. $Lt = 8$ seconds, physiological; basal microcirculation at rest diastole 6 seconds, systole 6 seconds), while in case of continuative ‘green’ therapy ALS G.A.R. $Lt = 12$ seconds and the microcirculatory activation still persists. The ‘type A’ class of treatments must continue forever and ever to prevent the resurgence of the Inherited Real Risk of brain disorder and of its pre-clinical degenerative evolutionary process (pre-metabolic syndrome) which could lead, soon or later, to the metabolic syndrome.

Conclusions

The physician, who knows QBS clinical diagnosis, can investigate the brain’s trigger-points in order to assess if there is any disease, potential, in progress or overt, even silent. The aspecific sign of ‘Inherited Real Risk’ of brain disorders allows the physician to make differential diagnosis between Inherited Real Risk of cerebral cancer, overt cerebral cancer and other neurodegenerative disorders. This diagnosis can be

refined with specific signs proper of the related cerebral disease, as the Inherited Real Risk of Amyotrophic lateral sclerosis (ALS), explained here in details.

QBS method allows an efficient pre-primary and primary prevention with recursive effects able to reverse the genetic alteration of mit-DNA and the mitochondrial cytopathy at the base also of oncological and neurodegenerative pathologies.

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¹ According to Tischendorf's concept of Angiobiotope (Curri, 1986), biological tissue-microvascular system can be described as formed by single units: the tissue-microvascular units. In its turn, the tissue-microvascular unit (T.M.U.) is made up by three fundamental components: 1) microvessels, diameter < 100 μ ; 2) the blood, flowing in them; 3) perivascular connective, periangium, interstitium or "environment" in which microvessels are placed, formed by water, free- and bound- water, cells and connective fibers, and interstitial matrix, glucosaminoglycans. Microvessels can be subdivided as follows (Pratesi, 1990): 1) Para-microcircle: small arteries and arterioles, according to Hammersen, venules of I, II, III order; shunts or Arterio-Venous Anastomoses (AVA), functionally speaking (Bucciante, 1949); 2) Microcircle: nutritional capillaries, post-capillaries venules, "meta"- arterioles. With the aid of QBS, doctor is able to evaluate, in dynamic manner, T.M.U. of every biophysical system, from both structural and functional viewpoint, according to a synergistic pattern, i.e., the clinical evaluation of microvascular dynamics. Notoriously the microvessels carry on a motor activity, autoctonous and deterministic chaotic, which represents one of the most remarkable manifestations of microcirculatory hemodynamics, characterized by a flow-motion and hematocrit rhythmically fluctuating due to the particular behaviour of both vasomotility and vasomotion. A biological system, as the tissue-microvessel system, so much highly evolved and well differentiated, as regards anatomy and physiology, cannot react to attacks, different in origin, which involve it, by a lot of ways. As far as tissue-microvessel unit is concerned, cells, transformed in smooth muscle cells and in ramified smooth muscle cells, when stimulated, either contract or dilate, although there is a residual possibility of further response. On the contrary, smooth muscle cells of the media of great arteries – elastic and muscular – which are less differentiated, react to various stimuli, even, de-differentiating and, then, evolving towards cells with secretory activity (Simonescu 1990, Gimbrone 1997). These concepts account for the reason of the restricted number of tissue-microvascular unit reactions, doctor can observe at the bed-side by biophysical semeiotics and Clinical Microangiology.

² According to Angiobiopathy theory, genome affects both micro-vessels and parenchyma. Investigating the microvessels, whose behavior is typical of dissipative systems far from equilibrium, this is a way to get indirect information from the state of health of their respective parenchyma.

³ This pre-clinical stage is not detectable through usual clinical tests, so it is necessary to explore new approaches, such as that introduced by QBS, which through bed-side evaluation, can diagnose the existence of pre-metabolic syndrome, that can last for years or decades, pre-clinical stage of the disease still potential or on training (evolution to pathology, pre- morbid state or gray area), so allowing an effective prevention. The pre-metabolic syndrome, as defined by Stagnaro, is the syndrome that precedes the metabolic one, and is linked with congenital real risks and their related QBS constitutions.

⁴ The IRR of brain disorders is nonspecific but becomes highly specific for its exact location.

⁵ Through QBS spleen and liver diagnosis, we can exclude Niemann Pick Disease (NPD) type A (intensive form of Acid Sphingomyelinase) and type B (light form of Acid Sphingomyelinase) if the intense pressure on spleen and liver does

not provoke a simultaneous gastric aspecific reflex (G.A.R.). Just in case of NPD type C there is an alteration of spleen and liver, as revealed by a simultaneous G.A.R. under the above mentioned manouvre.

Further, there is a characteristic QBS sign common for all NP types (A,B and C). A pressure of mean intensity exclusively upon the right and left temporal area provoke a G.A.R. after a latency time (Lt) of 4 seconds (the basal physiological Lt is 8 seconds) whose intensity is at least of 4 cm. In this last cases other QBS signs reveal the typical vasomotility and vasomotion's alteration of cholesterolic metabolism, as shown by the microcirculatory sign of hepatic steatosis.

⁶ The following remedies and healthy lifestyles belong to the class of 'type A' or 'green' therapy: etymologically speaking diet, i.e., Mediterranean diet and physical activity, histangioprotectors i.e., conjugated-melatonin, and others, i.e., LLLT, NIR-LED, prayer, meditation, etc.

⁷ The following treatments belong to the class of 'type B' or 'blue' therapy: quantum therapy able to capture and re-transmit customized frequencies from the human body in BRR, thermal sulfidric water.