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MULTIPLE SCLEROSIS, MITOCHONDRIA AND DIET THERAPY: AN OVERVIEW

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ABSTRACT Multiple sclerosis (MS) is defined as one chronic disease of central nervous system with neurodegenerative and inflammatory components, where most of the patients shown a relapsing-remitting course defined by the acute inception of focal neurologic deficits and consistent focal inflammatory changes visible on MRI. The causal factor of this complicated autoimmune and neurodegenerative disease is still unknown. Mitochondrial dysfunction is the key contributor to the neurodegenerative process of this disease. The current review signifies the possible potential role of mitochondria in MS and the different dietary approach as a disease modifier with the special emphasis on mitochondrial function and neurodegenerations.Research regarding therapeutic implementation of different diet in MS is advancing day by day; but currently remains with limited data. Few studies have been intended with meticulously collected observations, and the very few clinical trials that have been executed with insufficient sample size or length to adequately assess efficacy. More epidemiological and observational studies on dietary implementations were required

KEYWORDS : Multiple sclerosis, Mitochondria, Diet ,Central nervous system.

INTRODUCTION

Multiple sclerosis (MS) is defined as one chronic disease of central nervous system with neurodegenerative and inflammatory components, where most of the patients shown a relapsing- remitting course defined by the acute inception of focal neurologic deficits and consistent focal inflammatory changes visible on MRI [1].Incidents reflect inflammatory demyelinating lesions in the optic nerves, spinal cord, and brain, causes symptoms such as loss of vision, gait difficulty, weakness, bowel and bladder disturbances, numbness etc[1].Most of the patients of MS experience global symptoms like fatigue, depression, and cognitive changes. Early in the disease course inflammatory lesion formation, atrophy, neurodegeneration begins [2] and drives disability over time [3].The causal factor of this complicated autoimmune and neurodegenerative disease is still unknown. In many reports several cellular mechanisms have been proposed, that are genetic factors, viral infections, autoimmune attack, demyelination, mitochondrial dysfunction, free radicals production, ionic imbalance and cellular clearance system dysfunction leading to final neuron loss [4-11]. Such factors act either as a primary cause or secondary consequences of MS, anyhow in many cases they work together to cause the MS disease [4-11]. Across the world the ongoing effort of searching genetic loci, may cause vast majority of patients with MS may provide some important clues to understand the disease process. Eventually the principal role of the mitochondria in many important cellular functions especially energy production are nonnegotiable [12]. Thus it is reasonable that its dysfunction is the key contributor to the neurodegenerative process of this disease [12-14]. The current review signifies the possible potential role of mitochondria in MS and the different dietary approach as a disease modifier with the special emphasis on mitochondrial function and neurodegenerations.

Mitochondrial Functions In Neurons And MS:

In all multicellular eukaryotes, the mitochondria are the fundamental for metabolic homeostasis [13]. Especially in nervous system, the adenosine triphosphate (ATP) generated by mitochondria is required to establish reliable synaptic transmission and appropriate electrochemical gradients[14]. In different central nervous system disorders, several mitochondrial defects have been identified. Therefore upset of normal mitochondrial function is detrimental to cellular activity. Nerve cells are specifically dependent on mitochondria for calcium buffering and ATP production and, thus are highly susceptible to mitochondrial defects [15].In the course of metabolic distress, several pathological pathways are initiated in mitochondria, together with the opening of the mitochondria permeability transition pore (mPTP),outflow of cytochrome c into the cytoplasm, induction of programmed cell death, and mitophagy [16]. In reaction to the cellular damage, the accumulation of excessive Ca2+ occurs in the matrix and thereby set out as the principal trigger for opening of the mPTP, remains as a high-conductance channel [14].Although the molecular identity of this pore has yet to be specified, but cyclophilin D (CypD) is known to facilitate mPTP activation under physiologic conditions[15].Thus aperture of the mPTP results in an altered proton electrochemical gradient, furthermore compromised membrane potential and changes in pH gradient [15].The expansion of mitochondrial membrane permeability allows for the accumulation of ROS, resulting in more oxidative stress, causing a self-propagating chain reaction of cell membrane lipid peroxidation, as well as the destruction of membrane lipids along with significant tissue damage [16].Consequently the overall reduction of ATP generation take place, eventually leads to the initiation of the intrinsic apoptosis pathway and cell death [16]. In the course of the last decades, a significant amount of reports indicated the critical benefaction role of mitochondria and oxidative stress to both inflammatory and neurodegenerative aspects of MS pathogenesis [12].

Reports are existed in patients with MS and(Experimental Autoimmune Encephalitis) EAE mouse model, where mitochondrial DNA alterations, mitochondrial structural changes, defective mitochondrial DNA repair events, abnormal mitochondrial enzyme activities, mitochondrial gene expressions, increased free radical production and oxidative damage have been observed significantly[12].One recent observation of the sharp arrival of the free mitochondrial DNA in the serum of the patients with MS at the outset of the disease also supports above findings [17].In this case specifically the myelin-producing glial cells called oligodendrocytes are explicitly susceptible to oxidative stress and inflammatory mediators and are one of the crucial targets of MS [18-20].Thus mitochondrial dysfunction plays a key role in progressive Multiple Sclerosis. Hence according to Mao et al, mitochondrial-targeted and neuroprotective treatments, or combination of neuroprotection and immunomodulatory may represent new and correct approach of MS therapy [21].

Dietary Approaches Against MS And Mitochondrial Dysfunction:

The pathophysiology of MS is complex and yet to understood completely[22].MS was once considered strictly related to T cell dysregulation; although several components of the innate

and adaptive immune systems have now prove to be crucial to MS immunopathology [22].

Disease-modifying medications of MS are expensive [23] and have several side effects [24]. Due to the limitations of pharmacologic approaches, MS patients often seek non-pharmacologic interventions such as specialized diets and supplements etc [25].

Current available MS disease modifying therapeutic diets are effective at diminishing new lesions and clinical relapses; however, more specific and effective approach is needed that halt underlying neurodegeneration [25]. It has been observed that approximately 10 % of patient reports with progressive neurological decline from the onset [25]. Current available MS disease modifying therapies are effective in relapsing patients slow but do not halt this neurodegenerative process. Thus there is a great need of recognition of strategies that are able to protect against chronic demyelination and axonal/neuronal loss[26].The remyelination process come about spontaneously however is highly unpredictable between individuals and efficiency decreases over time [27].In adult brain, Oligodendrocyte precursor cells (OPCs) capable of remyelination are present, however, inhibitors of OPC differentiation in the local environment hinder this process [27].Thus therapeutic approach at manipulating the CNS environment to favor OPC differentiation and encourage remyelination could certainly be of benefit in MS[28].

Ketogenic Diet (KD) Mitochondrial Health And Multiple Sclerosis:

The century old KD is used to treat patients with pharmacological resistance to epilepsy [29-31]. Although the recent approach on implementation of KD is changing and has also been useful in some totally different diseases such as obesity [32], PCOS [33], cancer [34,35], diabetes [36], or other pathological conditions [37–39].Notably many previous reports have already pointed out the positive impact of KD on many neurological and neuromuscular diseases[40].

Nutritional Biochemistry Behind The Ketogenic Diet:

At initial stage of KD diet implementation, after a few days of drastic reduction in carbohydrate from the diet (below 20 gm /day), our glucose reserves become inadequate both for the supply of glucose to the CNS (central nervous system) and for natural fat oxidation through the contribution of oxaloacetate in the Krebs cycle [40,41]. The oxaloacetate is moderately unstable at normal body temperature and not be able to accumulated in the mitochondrial matrix [41]. Hence in such "glucose deprivation stage" the efficient oxaloacetate supply is needed for proper functioning of the tricarboxylic acid cycle.In this case the oxaloacetate is produced via the anaplerotic cycle, synthesizes oxaloacetate out-of glucose through ATP dependent carboxylation of pyruvic acid through pyruvate carboxylase [42].

In normal condition the central nervous system(CNS) cannot be able to utilize the free fatty acids(FFA) as one energy source(as FFA cannot be able to cross the blood-brain barrier),and can able to utilize only glucose as the energy source. During the "glucose deprivation" state the CNS finds out the alternative source of energy in the form of ketone bodies(KBs): acetoacetate (AcAc), 3-hydroxybutyrate (3HB), and acetone [40-46],acquired from the overproduction of acetyl-CoA without a concurrent supply of an sufficient oxaloacetic acid. This is called the 'ketogenesis' and principally it takes place in the mitochondrial matrix in the liver [47].During such "glucose deprivation" except all other cells, the hepatic cells and red blood corpuscles are unable to utilize ketones due to lack of the succinyl-CoA: 3-CoA transferase (SCOT) enzyme essential to convert acetoacetate into acetoacetyl CoA [46].In conditions when diet is producing enough glucose, the concentration of KBs is usually very low (<0.03mmol/L) compared to glucose (approx. 4 mmol/L) [48, 49].During Ketosis while the KBs cross the concentration of about 4 mmol/L (remains close to the kM for the monocarboxylate transporter[48]) they start to be utilised as energy source by the CNS and the glycaemia remains within physiological levels as the glucogenic amino acids and glycerol produced via lysis from triglycerides [50, 51].During the process of physiological ketosis (KD intake or starving) ketonemia come to maximum levels of 7/8 mmol/L with no changes in pH where as exclusively in uncontrolled diabetic ketoacidosis this can surpass 20 mmol/L with a concomitant reduction of blood pH [44, 52] .Thus for normal individual the blood levels of KBs never exceed 8 mmol/L as the CNS efficiently uses these molecules as energy supply in place of glucose [53].

Role Of KD In Normal Mitochondrial Functioning:

Ongoing reports are already proven the benefits of KD in improving mitochondrial functioning and stimulate mitochondriogenesis [54–57].Interestingly according to Wallace et al, "Ironically, one of the oldest therapeutic approaches—fasting and the ketogenic diet—remains the most promising treatment for mitochondrial defects" [58].Reports are also existing regarding the effects of KDs in mitochondriopathies. KD could be a safe and effective therapy that reduces seizures in children having intractable epilepsy and several respiratory complex defects (complex I, II, IV, or combined)[59].Again in mouse model[60],KD is treated for late-onset of mitochondrial myopathy ,the well known reason in humans autosomal dominant progressive external ophthalmoplegia, with weakness of muscle, assortment of generalized mtDNA deletions, and cytochrome c oxidase negative muscle fibers. The diet therapy decreased the amount of cytochrome c oxidase negative muscle fibers along with the prevention of the formation of mitochondrial ultra structural abnormalities in the muscle[60].They also observed that the diet cured most of the metabolic and lipidomic anomalies by inducing mitochondrial biogenesis. Even though the KD might be a therapeutic tool in several mitochondrial-based diseases, but still it is prophylactic that ketogenic diet therapy has several side effects. Thus proper modifications and strict observation is required during KD treatment [61].

Calorie Restriction (CR) Diet:

Caloric Restriction is another alternative approach, gained attention during present time [62]. CR is one type of dietary modifications to lower the calorie intake which has been shown to improve neuroprotection and attenuate neurodegenerative disorders. Specially in ageing literature rats fed highly calorie-restricted diet (66% food restriction) were protected from the progression of EAE ,as the endogenous corticosteroid production decrease in inflammatory cytokines, and rise in neurotrophic factors[63,64].According to Mojaverrostami et al, CR therapy can induce remyelination potential in a Cuprizone-demyelinating mouse model of MS by rising oligodendrocyte generation while reducing their apoptosis[65]Furthermore 40% calorie restricted diet in mice showed decreased EAE severity as well as lowered the inflammation, demyelination, and axonal damage [66].Another report on mouse model of MS shows that intermittent caloric restriction using the modified fasting-mimicking diet (FMD) was effective in the treatment of EAE through ameliorating inflammatory response and promoting recovery of the damaged tissue[65].Whereas the current challenges are to translating significant long-term caloric restriction to humans.

Mcdougall Diet:

Another dietary approach named McDougall diet, consists of very low-fat (<10%), starchy plant-based diet including fruits

and vegetables [122]. No foods from animal origin were allowed nor are oils permitted. In this randomized control trial 61participants with relapsing remitting MS (RRMS) were studied for the period of 12 months. Present dietary approach was well adhered to and tolerated, but it resulted in no significant improvement on brain MRI(the number of new T2 lesions on MRI, was not satisfactory), relapse rate or disability as assessed by expanded disability status scale (EDSS) scores in subjects with RRMS over one year[122]. There were significant improvements in measures of fatigue, BMI and metabolic biomarkers [122].

Mediterranean Diet (MD):

Reports are generating regarding positive impact of Mediterranean diet in MS[68-70]. MD are composed of restricted saturated fats, and rich in polyunsaturated & monounsaturated fats (especially fish and olive oil)[68].It is rich in fruits and vegetables, and low in processed foods implying low salt content. According to Gu et al, the level of adherence to MD has been associated with structural measures of neurodegeneration [71].According to Sedaghat et al, the high consumption of fruits and vegetables were significantly associated with reduction of MS risk in MD. According to Tobore et al, MD therapy, stress-relieving action, quit smoking and alcohol consumption, exercise, and peer support programs are the best way to treat the disease [69].

Paleolithic Diet

Another popular diet therapy in MS is the Paleolithic diet. NF-κB signaling pathway activation is one crucial step in any inflammatory response, resulting in initiation of inflammatory protein expressions[72]. Thus it is a ubiquitious protein responsible for regulation of cell signaling path ways in immune systems. Reports exist that -lipoic acid (ALA) and polyphenols present in Paleolithic diet (modified) have regulatory role in NF- B pathways[73].Typical Paleolithic diet consists of pasture-raised meats, fish, grass-fed, vegetables, fruits, roots, fungi and nuts; excludes grains, legumes, and dairy products; and limits refined sugars, starches, processed foods, and oils. Present diet is also rich in vitamins B, D, E, and K, polyunsaturated fatty acids, coenzyme Q10, -lipoic acid, polyphenols, carotenoids, zinc, and selenium. Overall it supports the mitochondrial function in addition to myelin growth and repair for MS patients[72].According to Irish et al, a Paleolithic diet can significantly improve the fatigue and quality of life in progressive multiple sclerosis (MS)[72].Thus it may be beneficial in the treatment and management of MS, by reduction in perceived fatigue, improvement mental and physical quality of life, increasing capacity to conduct exercises, and betterment hand and leg function of MS patients[72].

CONCLUSION:

Research regarding therapeutic implementation of different diet in MS is advancing day by day; but currently remains with limited data. Few studies have been intended with meticulously collected observations, and the very few clinical trials that have been executed with insufficient sample size or length to adequately assess efficacy. More epidemiological and observational studies on dietary implementations were required. Also the data regarding other behaviors such as smoking and physical activity, sedentary life styles should also be one big concerned with MS. Moving this field of research forward presents several challenges. Although at present several different dietary approaches are being applied worldwide, but interestingly these all have some common strategies. Avoidance of highly processed food, carbohydrate rich foods (high glycemic index), saturated fat restriction, salt restriction, more inclusion of plant based foods are some common measures in this case. However more systematic evaluation of dietary strategies in MS is required, while specialized diet therapy is the key therapeutic approach to manage MS degenerations.

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