Mitochondrial Dysfunction in Autistic Children and Oral Coenzyme Q10 Supplementation Treatment

Elham Mousavinejad1, Mohammad Ali Ghaffari1, Mohammad Reza Afsharmanesh1, Sahar Sadegh-Nejadi2, Wesam kooti3 and Reza Afrisham2*

1Department of Clinical Biochemistry, Faculty of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
2Department of Clinical Biochemistry, Faculty of Medicine, Tehran University of Medical Sciences, Tehran, Iran
3Student Research Committee, Kurdistan University of Medical Sciences, Sanandaj, Iran

Corresponding author: Afrisham R, Department of Clinical Biochemistry, Faculty of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran, Tel: +989331910231; E-mail: rezaafrisham@yahoo.com

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Introduction

Psychiatry disorders can have a threat on the society's health [1,2]. Autism spectrums of disorders (ASD) are considered neurodevelopmental disorders. In psychiatry, autism is characterized by ADI-R. Children who are affected by this disease usually suffer from impaired social interactions, speech disabilities, repetitive and/or compulsive behaviours, deficits in memory, learning, or other neurological functions, hyper-or hypo sensitivity to sensory stimuli, anxiety, and difficulty to adapt to new environments/habits [3]. Epidemiological studies has presented that the prevalence of ASD has increased in recent years. Due to the poor understanding of this disease, there has been no biomarkers identified as characteristic of autistic spectrum disorders and there is no certain treatment approach [4]. In the etiology of autism, several disturbances in biochemical and inflammatory factors have been observed. The etiology of ASD have been seen from genetic, neurological and environmental factors, like oxidative stress, and its clinical implications in ASD is now of particular interest [4,5]. Recent studies have shown alterations in immuno-inflammatory autistic individual's system. High levels of post-mortem individuals with autism revealed high levels of tumour necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin 1-beta (IL-1β) in addition studies conducted on brain tissue and cerebrospinal fluid [6,7].

Mitochondrial dysfunction (MtD) is likely precipitated by oxidative stress and inflammatory response, and could contribute to a number of diagnostic symptoms and comorbidities of ASD (abnormal energy metabolism, chronic gastrointestinal problems, and abnormalities in fatty acid oxidation). It was thought one day that MtDs is rare, but today they are regarded as one of the most common metabolic disorders, stress oxidative and inflammation response in children [8]. Classical mitochondrial dysfunctions occur in a subset of ASD cases and are usually caused by genetic anomalies or mitochondrial respiratory pathway abnormalities [9]. In addition, they have also been associated with different behaviours in children. There have been many studies that reveal evidence of mitochondrial dysfunction (MtD) in children with ASD. Various drugs of either synthetic or natural origin applied in the treatment of brain disorders need to cross the BBB before they can be used in Alzheimer’s disease, Parkinson’s disease, autism, and many other chronic illnesses. This review suggests that a Coenzyme Q10 supplement is a reasonable MtD therapy to consider for most children diagnosed with Autism.
Mitochondrial Dysfunction (MtD) in Autistic Children

In 1959, the first disorder of mitochondrial function was described by Luft [18]. On the other hand, the true incidence and prevalence of mitochondrial disorders and dysfunction remain unclear [19]. The nervous system is the most commonly affected system in mitochondrial disorders [20]. The most of MtD of children present with neurologic signs and patients demonstrate intellectual dysfunction or psychiatric disturbances [21]. If the recognition of mitochondrial disorders in children is considered challenging, their diagnosis in childhood is even more challenging [22]. Lactic acidosis is considered the most recognized laboratory abnormality in patients with mitochondrial disorders. A Dysfunction in the electron transport chain causes a decrease in the production of adenosine triphosphate. When lactic acidosis is present, consideration must be given to the fact that it is not specific to mitochondrial dysfunction. Elevated serum levels of lactate can be seen with neurodegenerative diseases, seizures and metabolic disorders [23]. During the initial evaluation, investigations for autistic disorders that may mimic mitochondrial disorders should be undertaken. The electron transport chain is part of a complex energy generating system inside cells [24]. An overall decrease in mitochondrial functions may result from defects in other systems. Plasma amino acids, urine amino and organic acids, pyruvate and acylcarnitine profiles are usually included in metabolic studies [25]. Elevations of protein, lactate, pyruvate and even white blood cells were demonstrated in the cerebrospinal fluid of patients with mitochondrial dysfunctions and autistic children [26]. In addition, MtD and oxidative stress may explain the high boy to girl ratio found in autism due to increased boy’s vulnerability to these dysfunctions. Mitochondrial dysfunction’s Biomarkers have been identified, but they seem widely under-utilized despite the available therapeutic interventions [27].

Potential Treatments of MtD in Autistic Children; Antioxidant and Anti-inflammatory Compounds

The more adept clinicians become at recognizing mitochondrial dysfunction in ASD, the more opportunities there will be for improving and ultimately treating the diagnosis. The severity of symptoms might differ, it is essential that most symptoms have to be addressed as soon as possible [28]. Some of the most important behavioral and social treatment approached for ASD [29].

Nutritional supplementation are given to improve reduced oxidative stress and inflammatory along with factors to improve decreased ER stress and mitochondrial ROS in autistic children [30]. Once effective treatment for MtD is implemented, the underlying pathophysiology and autistic symptoms in affected individuals would be expected to either improve or cease worsening [31]. Moreover, potentially effective drugs and vitamins/supplements are used most often in the treatment of ASD children [32]. In recent studies using anti-oxidant compounds showed a significant improvement in social interaction and communication using the Aberrant Behavior Checklist (ABC) scale of patients with ASD. Some antioxidants used in patients found no difference on the total ABC, but instead a significant improvement on the clinical laboratories [33]. In many of the randomized, placebo-controlled studies, the dose of antioxidant compounds added to nutrition autism had an effect on total ABC, but decreased the irritability subscale [34]. Recently, studies have reported that patient with ASD and who are treated with anti-inflammatory compounds showed the most improvement in social interaction and communication and decreased serum TNF-a and IL-6 levels [35,36]. These results indicate that subgroups of children with ASD, who are most amenable to treatment with anti-inflammatory compounds, may be identified by objective inflammation. This study recently showed that anti-inflammatory compounds have a better bioavailability [37]. Therefore, it could be developed for the treatment of ASD. By inhibiting cyclooxygenase-1 (COX-1), various plant compounds can have anti-inflammatory activities [38]. The local increase in oxidative is resulted from the accumulation of COX-1 enzyme in microglia in ASD patients. The use of immuno-modulatory treatments has been considered for children diagnosed with ASD [39]. These compounds are shown to mimic brain-derived neurotrophic factors (BDNF) and inhibit microglial activation and proliferation, which reduced symptoms in focal brain inflammation [40].

Moreover, they improved memory in ASD and inhibited autism-like behavior [14,37,41,42]. Unfortunately, there are few clinically approved anti-inflammatory drugs that can be used in children with ASD.

Coenzyme Q10 Supplementation Treatment; Reduced Oxidative Stress and Inflammation

Coenzyme Q10 (CoQ10) and reduced nicotinamide adenine dinucleotide (NADH) are common antioxidant supplements that effect the central nervous system (CNS), which have been used for several decades as dietary supplements for general health maintenance. The major form of CoQ10 is the reduced form ubiquinol (Qx), which is responsible for its antioxidant properties. CoQ10 increases the cellular ATP production via mitochondrial oxidative phosphorylation, and their supplementation could help improve fatigue and other symptoms in CFS [43]. The potential anti-inflammatory effect of CoQ10 or its reduced form has been suggested through in vitro and in vivo studies [44]. For instance, Q10 was able to decrease the inflammatory score based on the mRNA level of TNF-α, interleukin-6, C reactive protein, STAMP2 and NADPH oxidase [45-47]. Coenzyme Q10 is required for Voltage Dependent Anion Channel (VDAC) ferricyanide reductase activity as proposed. The requirements required for coenzyme Q for the function of a pore protein, such as VDAC, is not without precedence; for example, binding of coenzyme Q to the UCP in the mitochondria is required for optimal function [48].

Several studies have shown that there is the MtD which reduces the rate of ATP synthesis and is the central agent of energy production in most CFS Autism spectrum disorders [23,49,50]. For its part, CoQ10 supplementation has been evaluated in many illnesses [51-53], such as with chronic diseases [54], but few studies have been published neuropsychiatric conditions and fibromyalgia.

CoQ10 is a naturally occurring flavonoid with potent antioxidant, anti-inflammatory properties that are found in green plants, herbs, and seeds [44]. Autism Spectrum Disorders are characterized by protein aggregates and inflammation as well as oxidative stress in the central nervous system (CNS) [55]. Multiple biological processes are linked to ASD such as depletion or insufficient synthesis of neurotransmitters, oxidative stress, and abnormal mitochondrial function. Furthermore, damaging of the blood brain barrier (BBB) in the CNS can also lead to various ASD children [56].

The inflammation markers were shown to be increased in the brain of many ASD patients including IL-1β and TNF-α, molecules secreted from mast cells, as well as MCP-1 and IL-8, which are chemotactic for Mast Cells. In particular, plasma levels of IL-8 and IL-6 were increased in children with ASD. IL-6 and TNFα- could disrupt the BBB and cause “focal encephalitis” in specific brain areas, thus contributing to the pathogenesis of ASD [57]. Anti-oxidant supplementation, which is a therapeutic strategy in treating this neurological disorder, could have positive clinical benefits [58]. The various drugs of either synthetic or natural origin applied in the treatment of brain disorders need to cross the BBB before they can be used on patients diagnosed with Alzheimer’s disease [59], Parkinson’s disease [60], autism [61] and many other chronic illnesses [62]. Even though synthetic drugs are used for the management of neurodegenerative disorders, they still have many side effects CoQ10 are seen to be having promising therapeutic agents because many dietary supplements have anti-inflammatory, antioxidative, as well as anticholinesterase activities. It has been suggested that these molecules may modulate the autonomic function by regulating the synthesis of endogenous catecholamines and acetylcholine [63]. Many researchers have been inclined towards natural compounds, which may have benefits and have minimal side effects.

Dietary Sources of Coenzyme Q10

All organisms, including humans, can synthesize ubiquinones. Foods such as rapeseed (canola), fish, meats, oils and sesame are good nutritional sources of CoQ 10, while lower levels can be originated in most fruits, dairy foods, cereals and vegetables [64]. Levels over 50 mg/kg may be found in beef, pork, and chicken liver and heart. Also, oils of vegetable are completely rich in CoQ10. Grape, Broccoli and cauliflower are diffident bases of CoQ10. Most berries and fruit signify a poor-to-very-poor source of CoQ10, excluding avocado, that has a comparatively elevated CoQ10 [65].

Dietary Sources of Antioxidants

Anti-oxidant supplementation is a therapeutic strategy in treating neurological disorders. This supplementation is such as herbs rich in polyphenols. Among these plants are Heracleum persicum and Ziziphus jujuba [66], fennel (Foeniculum vulgare) [67], celery (Apium graveolens) [68-70] that have antioxidant properties.

Conclusion

However, today the etiology of ASD is poorly understood. Potential mechanisms that may link MtD to neuronal dysfunction, clinical symptoms, pathogenesis of autism include stress oxidative, immune and inflammatory response. MtD can be diagnosed via certain biomarkers and is potentially treatable. Therefore, increased efforts of MtD screening of all individuals affected with autism should be encouraged. The purpose of this systematic review was to provide a mechanism of the therapeutic intervention strategies, like Co-Q10 supplementation, in treating ASD children with MtD, could have positive clinical benefits. In the future, oral Co-Q10 supplementation could be used as a promising therapeutic treatment for ASD children, due to their anti-inflammatory and antioxidative, as well as their anticholinesterase activities.

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References


