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Coenzyme Q10 deficiency in myalgic encephalomyelitis / chronic fatigue syndrome (ME/CFS) is related to fatigue, autonomic and neurocognitive symptoms and is another risk factor explaining the early mortality in ME/CFS due to cardiovascular disorder

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Abstract

INTRODUCTION: Myalgic encephalomyelitis / chronic fatigue syndrome (ME/CFS) is a medical illness characterized by disorders in inflammatory and oxidative and nitrosative (IO&NS) pathways.
METHODS: This paper examines the role of Coenzyme Q10 (CoQ10), a mitochondrial nutrient which acts as an essential cofactor for the production of ATP in mitochondria and which displays significant antioxidant activities.
Plasma CoQ10 has been assayed in 58 patients with ME/CFS and in 22 normal controls; the relationships between CoQ10 and the severity of ME/CFS as measured by means of the FibroFatigue (FF) scale were measured.
RESULTS: Plasma CoQ10 was significantly (p=0.00001) lower in ME/CFS patients than in normal controls. Up to 44.8% of patients with ME/CFS had values beneath the lowest plasma CoQ10 value detected in the normal controls, i.e. 490 µg/L. In ME/CFS, there were significant and inverse relationships between CoQ10 and the total score on the FF scale, fatigue and autonomic symptoms. Patients with very low CoQ10 (<390 µg/L) suffered significantly more from concentration and memory disturbances.
DISCUSSION: The results show that lowered levels of CoQ10 play a role in the pathophysiology of ME/CFS and that symptoms, such as fatigue, and autonomic and neurocognitive symptoms may be caused by CoQ10 depletion.
Our results suggest that patients with ME/CFS would benefit from CoQ10 supplementation in order to normalize the low CoQ10 syndrome and the IO&NS disorders. The findings that lower CoQ10 is an independent predictor of chronic heart failure (CHF) and mortality due to CHF may explain previous reports that

the mean age of ME/CFS patients dying from CHF is 25 years younger than the age of those dying from CHF in the general population. Since statins significantly decrease plasma CoQ10, ME/CFS should be regarded as a relative contraindication for treatment with statins without CoQ10 supplementation.

INTRODUCTION

Myalgic Encephalomyelitis or Chronic Fatigue Syndrome (ME/CFS) is a medical disorder, characterized by profound fatigue, inflammatory, autonomic and neuropsychiatric symptoms. According to the Center for Disease Control and Prevention (CDC) criteria (Fukuda *et al.* 1994) a patient must satisfy two criteria in order to receive a diagnosis of ME/CFS: a) suffer from severe chronic fatigue lasting at least six months, while no known medical condition may explain the fatigue; and b) the presence of at least four of the following symptoms, substantial impairment in short – term memory or concentration; sore throat; tender cervical and axillary lymph nodes; muscle pain; multi – joint pain without selling or redness; headache of new type; unrefreshing sleep; and post exertion malaise lasting more than 24 hours. Despite the medical nature of ME/CFS many doctors and governments still consider "CFS" as a mental condition - not even a disorder - and treat those patients accordingly with cognitive behavioural therapy and graded exercise treatment (Twisk and Maes, 2009; Maes and Twisk, 2009).

There is now abundant evidence that ME/CFS, as defined above, is characterized by various disorders in inflammatory and oxidative and nitrosative stress (IO&NS) pathways (Maes, 2009; Maes *et al.* 2007a; 2007b; 2007c; Lorusso *et al.* 2009; Aspler *et al.* 2008; Kerr *et al.* 2008; Buchwald *et al.* 1997; Nijs en de Meirleir, 2005). The key phenomena explaining induction of the IO&NS pathways appear to reside in the white blood cells, which show an increased production of nuclear factor kappa B (NFκB), cyclo-oxygenase-2 (COX-2) and inducible NO synthase (iNOS) (Maes *et al.* 2007b; 2007c; Maes, 2009). Increased O&NS in ME/CFS is indicated by - amongst other things - higher isoprostane; oxidized low density lipoproteins (LDL); LDL thiobarbituric acid reactive substances (TBARS); and protein carbonyl levels (Vecchiet *et al.* 2003; Kennedy *et al.* 2005; Jammes *et al.* 2005; Smirnova and Pall, 2003). Damage by O&NS to functional proteins and membrane fatty acids in ME/CFS is evidenced by increased IgM-mediated immune responses against membrane fatty acids, by-products of lipid peroxidation (MDA and azelaic acid), and NO derivates, such as nitro-tyrosine, nitro-phenylalanine, and nitro-tryptophan (Maes *et al.* 2006b; 2007e; 2008).

We have discussed that induction of the above-mentioned IO&NS pathways may cause the symptoms experienced by ME/CFS patients. Thus, intracellular inflammation with an increased production of COX-2 and iNOS may cause aches and pain, muscular tension, fatigue, irritability, sadness, and the subjective feeling of infection, whereas O&NS and the damage caused by O&NS may cause aches and pain, muscular tension and fatigue (Maes, 2009; Maes *et al.* 2006b; 2007b; 2007c; 2007d; 2008). The above IO&NS pathways in ME/CFS may be induced by a number of trigger factors, such as bacterial and viral infections, bacterial translocation through increased gut permeability, psychological stressors and physical exhaustion (Maes, 2009).

Another potential factor that may participate in the pathophysiology of ME/CFS is low Coenzyme Q10 (CoQ10). CoQ10 is an essential component of the mitochondrial respiratory chain (Butler *et al.* 2003), a strong anti-oxidant, that confers resistance to mitochondrial damage by O&NS (Chaturvedi and Beal, 2008), and an anti-inflammatory agent (Schmelzer *et al.* 2007a; 2007b; 2008). Low-energy syndromes are often accompanied by a depletion of CoQ10, e.g. the Prader-Willi syndrome, Friedrich's ataxia, Steinert's myotonic dystrophy, cardiac and skeletal muscle dysfunctions, cancers, and hereditary mitochondrial disorders (Butler *et al.* 2003; Cooper *et al.* 2008; Siciliano et al.. 2001; Rusciani *et al.* 2006). In those patients with low energy syndromes, CoQ10 supplementation increases plasma CoQ10 and energy as well (Cooper *et al.* 2008; Bonakdar and Guarneri, 2005; Singh *et al.* 2003). In patients with unexplained fatigue, the treatment that best predicts fatigue improvement is CoQ10 supplementation (Bentler *et al.* 2005). There are, however, to the best of our knowledge, no studies in ME/CFS examining plasma CoQ10 concentrations.

The present study has been carried out in order to examine plasma CoQ10 levels in patients with ME/CFS and to examine its relationships with specific ME/CFS symptoms.

SUBJECTS AND METHODS

Subjects

Eighty subjects participated in this study, i.e. 22 healthy volunteers and 58 patients suffering from ME/CFS. All ME/CFS subjects were outpatients admitted to the Maes Clinics, Antwerp, Belgium. We made the diagnosis of ME/CFS by means of the Centres for Disease Control and Prevention (CDC) criteria (Fukuda *et al.* 1994). In order to measure the severity of illness and to examine the symptoms correlates of lowered CoQ10 we have employed the Fibromyalgia and Chronic Fatigue Syndrome Rating Scale (FF scale) (Zachrisson *et al.* 2002). The FF scale measures 12 symptoms, i.e. pain, muscular tension, fatigue, concentration difficulties, failing memory, irritability, sadness, sleep disturbances, autonomic disturbances, irritable bowel, headache, and subjective experience of infection. The total sum on this scale was employed as a measure of the severity of illness.

We have excluded all subjects with life-time diagnoses of psychiatric DSM IV-R disorders, e.g. depression,

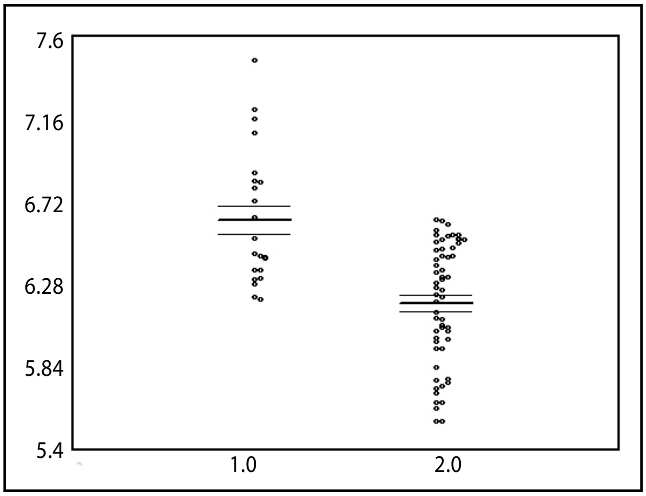

Figure 1. Scatter plot of the measurements of Co-enzyme Q10 (in ln transformation) in 58 patients with myalgic encephalomyelitis / chronic fatigue syndrome (2.0) and 22 normal volunteers (1.0).

bipolar, anxiety, psychotic, substance use and organic mental disorders. Any subjects with medical illnesses were omitted from this study, e.g. inflammatory bowel disorders, diabetes type 1 or type 2, hypertension, and arteriosclerosis. We excluded subjects with abnormal blood tests, such as alanine aminotransferase (ALT), alkaline phosphatase (ALP), blood urea nitrogen (BUN), calcium, creatinine, electrolytes, thyroid stimulating hormone (TSH), total protein and positive IgM antibody titers for EBV or CMV. We were careful in omitting patients and controls who were treated with statins and beta-blockers and who had been taking dietary supplements with CoQ10. We have excluded any subjects who had ever been treated with anti-psychotic drugs, anticonvulsants or mood stabilizers and subjects who had been taking other psychotropic drugs during the last year prior to the studies. Other exclusionary criteria for patients and controls were acute infections for at least 2 months prior to the study. Patients and controls gave written informed consent after the study protocol was fully explained; the study has been approved by the local ethical committee.

Methods

Plasma CoQ10 was determined using a HPLC method manufactured by Chromsystems Diagnostics (Munich, Germany). This reagent kit allows the reliable chromatographic determination of CoQ10 in an isocratic HPLC run using UV detection (275 nm). CoQ10 is released by precipitating the proteins and then concentrated using solid phase extraction. Inclusion of an internal standard minimizes any analytical variation. We followed the instructions as provided by Chromsystems Diagnostics (see: http://www.chromsystems.com/Description.103.0.html?&L=1) The Intra-assay coefficient of variation (CV) was < 5%, and the inter-assay CV < 6%.

Statistics

Differences between group means were assessed by means of analysis of variance (ANOVA) or covariance (ANCOVA). Relationships between variables were ascertained by means of Pearson's product-moment correlation coefficients and regression analyses. Stepwise discriminant multiple ANOVA (MANOVA) with an F-to-enter of p=0.05 was used to assess the symptomatic characteristics of different groups. The independence of classification systems was ascertained by means of analysis of contingence tables (χ^2-test) and Fisher's exact probability test. The significance was set at α=0.05 (two tailed).

RESULTS

There were no significant differences in age (F=3.7, df=1/94, p=0.06) between normal controls (mean age ±SD=45.4 ±10.1 years) and ME/CFS patients (38.5 ±13.9 years). There was no significant difference (χ^2 =0.9, df=1, p=0.3) in gender distribution between normal controls (5 male/17 female) and ME/CFS patients (8 male/50 female patients). There were no significant correlations between CoQ10 and age, either in the controls (r=0.21, p=0.6) or ME/CFS patients (r=0.06, p=0.7). There were no significant (point-biserial) correlations between CoQ10 and gender, either in the controls (r=0.07, p=0.8) or ME/CFS patients (r=-0.02, p=0.9).

Figure 1 shows the CoQ10 values in patients and controls. ANOVA showed that serum CoQ10 was significantly lower in ME/CFS patients than normal controls (F=31.0, df=1/78, p=0.00001). Covarying for age and sex in an ANCOVA did not change these results (F=25.9, df=1/76, p=0.00003). Neither age (F=0.8, p=0.6), nor gender (F=0.09, p=0.7) were significant in this ANCOVA.

There was a significant and negative correlation between serum CoQ10 and the total score on the FF scale (r=-0.28, p=0.03). Regression analyses of plasma CoQ10 on each of the 12 FF items showed that there were significant and inverse correlations between CoQ10 and fatigue (r=-0.86, $p<10^{-5}$) and autonomic symptoms (r=-0.36, p=0.005).

We have divided the ME/CFS study group in two subgroups according to their CoQ10 values, i.e. lower or higher than 490 µg/L, that is the lowest value observed in the normal controls. Up to 26 patients had values lower than 490 µg/L (mean CoQ10=361.7 ±68.2 µg/L), while 32 patients had values higher than 490 µg/L (mean=624.4 ±72.6 µg/L). Stepwise discriminant MANOVA showed that two FF items displayed a significant discriminatory power, i.e. fatigue and irritability (F=33.5, df=1/56, p=0.00001; the distance between both centroids being 1.53 SDs. Finally, we have divided the ME/CFS patients in two groups according to the q25 values for CoQ10 in the ME/CFS group, i.e. 390 µg/L. There were 14 patients with very low (<390 µg/L) plasma CoQ10 versus 44 patients with plasma CoQ10 > 390 µg/L. Patients with very low plasma CoQ10 (<390 µg/L) had significantly greater scores on four FF items, i.e. fatigue ($F=66.5$, $df=1/56$, $p<10^{-6}$), autonomic symptoms ($F=10.5$, $df=1/56$, $p=0.002$), and concentration ($F=4.0$, $df=1/56$, $p=0.04$; means: 3.2 ± 1.3 versus 2.4 ±1.2) and memory ($F=5.2$, $df=1/56$, $p=0.02$; means 3.7 ±1.1 versus 3.0 ±1.0) disturbances.

DISCUSSION

This is a first study which shows that ME/CFS is accompanied by significantly reduced plasma concentrations of CoQ10 and that lowered plasma CoQ10 is related to specific symptoms of ME/CFS, such as fatigue, autonomic and neurocognitive symptoms.

The first major finding of this study is that ME/CFS is characterized by a highly significant depletion in plasma CoQ10. Up to 44.8% of all patients had plasma CoQ10 values that were lower than the lowest CoQ10 value established in normal controls, i.e. 490 µg/L. These findings show that many patients with ME/CFS exhibit a "low CoQ10 syndrome".

This CoQ10 depletion in ME/CFS patients may be involved in the different pathophysiological pathways, which underpin ME/CFS.

* First, plasma CoQ10 depletion in ME/CFS may result in impaired antioxidative protection which in turn may enhance induction of the O&NS pathways and, consequently, damage to membrane fatty acids and functional proteins (Maes, 2009). Indeed, the antioxidant properties of CoQ10 explain its protective, including neuroprotective, properties whereby CoQ10 protects against neuronal damages (Chaturvedi and Beal, 2008; Young *et al.* 2007; Li *et al.* 2005; Matthews *et al.* 1998). The present findings reinforce the existent literature showing that ME/CFS is accompanied by a decreased antioxidant status, as evidenced by lower serum zinc and dehydroepiandrosterone sulfate (Maes *et al.* 2005; 2006a).

* Second, mitochondrial constituents, such as CoQ10, prevent the generation of free radicals during the oxidative processes in the mitochondria and thus confer resistance to mitochondrial damage by O&NS (Chaturvedi and Beal, 2008; Liu, 2008). Recently, mitochondrial dysfunctions have been established in ME/CFS. Behan et al. (1991) examined muscle biopsies of 50 patients with post-viral fatigue syndrome (a variant of ME/CFS) and found branching and fusion of mitochondrial cristae in 35 specimens and mitochondrial degeneration with swelling, vacuolation, myelin figures and secondary lysosomes in 40 samples. Lane et al. (1998) reported that ME/CFS patients with abnormal lactate responses to exercise had a significantly lower proportion of mitochondria rich type 1 muscle fibers.

* Third, the anti-inflammatory effects of CoQ10, such as downregulation of NFκB-gene expression (Schmelzer *et al.* 2008), suggest that a deficiency of CoQ10 may aggravate the intracellular inflammatory processes in ME/CFS characterized by increased NFκB production (Maes, 2009; Maes *et al.* 2007a). CoQ10 may also reduce the production of pro-inflammatory cytokines, such as tumor necrosis factor alpha (Schmelzer *et al.* 2007a), which production is known to be disturbed in ME/CFS (Patarca *et al.* 1994).

* Fourth, CoQ10 may counteract the induction of the IO&NS pathways by endoxin or LPS (Sugino *et al.* 1987; Abd El-Gawad and Khalifa, 2001). This is of importance to ME/CFS since leaky gut and a consequent gut-derived inflammation with a mounted inflammatory response against LPS of enterobacteria are new pathways in ME/CFS (Maes and Leunis, 2008; Maes *et al.* 2007a; 2007d).

* Last but not least, CoQ10 is an obligatory element in the electron transport chain (ETC) within the mitochondria, which produces much of the ATP that powers the energy in our cells and our body (Butler *et al.* 2003; Crane, 2001). On the inner membrane of the mitochondria, CoQ10 transfers electrons from complexes I and II to complex III which take part in the respiratory chain and the synthesis of ATP (Dutton *et al.* 2000). In this respect, it has been hypothesized that most if not all ME/CFS patients suffer from insufficient energy due to cellular energy dysfunction (Myhill *et al.* 2009). In the next paragraph we will discuss that the low CoQ10 syndrome in ME/CFS is indeed characterized by a loss of energy.

The second major finding of this study is that there are significant inverse correlations between plasma CoQ10 and specific symptoms such as fatigue and autonomic symptoms and that ME/CFS patients with very low plasma CoQ10 suffered significantly more from fatigue, autonomic symptoms, and concentration and memory disorders.

Our findings that low plasma CoQ10 is a strong determinant of fatigue is in agreement with previous findings that a depletion of plasma CoQ10 by treatment with statins, may induce fatigue, which is reversible upon supplementation with CoQ10 (Langsjoen *et al.* 2005; Passi *et al.* 2003). Indeed, treatment with statins may reduce the synthesis not only of cholesterol but also of CoQ10. This is because statins block HMG-CoA reductase of the mevalonate pathway, which is needed for the synthesis of the isoprene side chain of CoQ10 (Mabuchi *et al.* 2005; Chu *et al.* 2006). Statins cause a 40% reduction in the plasma levels of CoQ10 reducing plasma CoQ10 to levels that are similar to those that we have found in our patients. The plasma CoQ10 concentrations found in our ME/CFS patients are thus in the range that can cause the symptoms of a "low CoQ10 syndrome". Our results also concur with other reports that low plasma CoQ10 in other disorders, such as autosomal recessive CoQ10 deficiency, mitochondrial disorders, Prader-Willi syndrome are often characterized by fatigue and exercise intolerance, which are treatable by CoQ10 supplementation (Butler *et al.* 2003; Siciliano *et al.* 2007; Gempel *et al.* 2007; Sobreira *et al.* 1997). Our results on a significant relationship between CoQ10 and fatigue are in agreement with other reports that a) the percentage of subjects with unexplained fatigue who found treatment with different supplements helpful was greater for coenzyme CoQ10 than for all other supplements (Bentler *et al.* 2005); and b) treatment with CoQ10 of patients after acute myocardial infarction showed that fatigue was more common in the control group than in the CoQ10 treated group (Singh *et al.* 2003).

We found that very low plasma CoQ10 concentrations appear to predict the occurrence of neurocognitive disorders. These findings concur with those of previous reports showing that lowering of plasma CoQ10 by treatment with statins is accompanied by significant memory loss, which was relieved by treatment with CoQ10 (Langsjoen *et al.* 2005). Moreover, CoQ10 has a clinical efficacy in improving neurocognitive disorders that are caused by reducing mitochondrial dysfunctions via O&NS pathways (Liu, 2008). Male intracerebroventricular-streptozotocin infused Wistar rats show a significant loss of cognitive performance and simultaneous signs of O&NS and a decline in hippocampal and cortex ATP (Ishrat *et al.* 2006). Treatment of those Wistar rats with CoQ10 reversed the neurocognitive impairments and the damage by O&NS in the hippocampus and the cortex.

In our study, lowered plasma CoQ10 was also correlated to the presence of autonomic symptoms. Since, the modulatory effects of CoQ10 on the autonomic activity are only recently detected (Zheng and Moritani, 2008) it is not clear yet whether a causal relationship underpins this statistical correlation. However, lowering plasma CoQ10 by statins may induce peripheral neuropathies that are reversible upon treatment with CoQ10 (Langsjoen *et al.* 2005). Although, lowering of CoQ10 levels by statins is also accompanied by a significant myalgia, the present study was unable to detect any correlations between the low CoQ10 syndrome in ME/CFS and FF symptoms, such as aches and pain and muscle tension. Previously, we have discussed that an increased production of iNOS and COX-2 and increased damage by O&NS may explain the occurrence of those symptoms in ME/CFS (Maes, 2009).

The low CoQ10 syndrome in ME/CFS may have very important medical consequences. It is well known that a deficiency of coenzyme Q10 is a possible cause of cardiac disease, such as chronic heart failure (CHF), and is an independent predictor of mortality in CHF patients (Molyneux *et al.* 2008). Moreover, there is evidence to support the therapeutic value of CoQ10 as an adjunct to standard medical therapy in congestive heart failure (Singh *et al.* 2007). CoQ10 has been shown to enhance systolic function, left ventricular ejection fraction and myocardium contractility in CHF (Sander *et al.* 2006; Belardinelli *et al.* 2005) and to improve the endothelium-dependent relaxation and endothelium-bound extracellular superoxide dismutase (Tiano *et al.* 2007). CoQ10 is also considered to be a protective factor for coronary artery disease (Yalcin *et al.* 2004). The abovementioned results may explain the previous finding of Jason et al. (2006) that the mean age of ME/CFS patients dying from heart failure, i.e. 58.7 years, is significantly lower than the age of those dying from heart failure in the general US population, i.e. 83.1 years. Thus, the low CoQ10 syndrome together with the induced IO&NS pathways are probably highly significant risk factors explaining the early mortality due to CHF in ME/CFS patients.

In the same study (Jason *et al.* 2006), the mean age of the ME/CFS patients dying from cancer, i.e. 47.8 years, was considerably lower than that of those dying from cancer in the general US population, i.e. 72.0 years. It can be hypothesized that the low CoQ10 syndrome in ME/CFS may increase the risk toward this earlier mortality due to cancer in ME/CFS. Indeed, low CoQ10 occurs in patients with various grades of cervical intraepithelial neoplasia and cervical cancers, while an inverse association was detected between plasma CoQ10 and histological grades of epithelial lesions (Palan *et al.* 2003. There are some reports that baseline plasma CoQ10 is a powerful and independent prognostic factor that can be used to estimate the risk for melanoma progression (Rusciani *et al.* 2006).

In conclusion, ME/CFS is characterized by significantly lower plasma concentrations of CoQ10. The latter appear to determine to a great extent the incidence of fatigue in those patients. Very low CoQ10 may also be involved in causing neurocognitive disorders and maybe autonomic symptoms. The results of our study and those of previous studies reporting on the treatment of the low CoQ10 and low energy syndrome and unexplained fatigue with CoQ10 suggest that patients with ME/CFS should be treated with CoQ10 in order to normalize their low plasma CoQ10 and the disorders in the IO&NS pathways as well.

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