

Research Paper: Coenzyme Q10 Insufficiency Contributes to the Duration and Frequency of Seizures in Epileptic Patients



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ABSTRACT

Introduction: Oxidative stress has recently emerged as a possible mechanism in the pathogenesis of epilepsy. Coenzyme Q10 (CoQ10) is a strong endogenous antioxidant that protects cells from lipid oxidation and Reactive Oxygen Species (ROS) production; however, the impact of CoQ10 on seizure characteristics in epileptic patients is unclear.

Methods: The current study enrolled patients with Epileptic Seizure (ES) to evaluate their serum concentration of CoQ10 and to investigate whether a relationship exists between CoQ10 levels with the duration, frequency, and type of seizure.

Results: A total of 39 patients with epileptic seizures and 35 healthy controls were included in the study. The levels of CoQ10 in ES patients were significantly lower in comparison with healthy controls (11.99±5.93 vs (ng/ml). 16.48±4.20 (ng/ml) P<0.001). We also found that the duration of epilepsy and seizure frequency was negatively correlated with serum CoQ10 levels.

Conclusion: These findings indicate that CoQ10 deficiency might substantially contribute to the clinical signs of epileptic patients.

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Highlights

- CoQ10 deficiency plays a role in the pathogenesis of Epileptic Seizure (ES).
- Decrement of CoQ10 level in ES may be contributed to an increase in the frequency and duration of the seizure.
- There is no association between the type of seizure and CoQ10 levels in epileptic patients.

Plain Language Summary

Decreasing antioxidants plays an important role in the pathogenesis of epilepsy. Coenzyme Q10 (CoQ10) is a strong endogenous antioxidant that protects the body against several diseases; however, the impact of CoQ10 in epilepsy is unclear. We evaluated the serum concentration of CoQ10 to test if there is any relationship between CoQ10 levels and clinical manifestation of seizure. We found that the levels of CoQ10 in epileptic patients were significantly lower compared to healthy volunteers. We also found that the clinical manifestation of the seizure (duration of epilepsy and seizure frequency) were negatively correlated with serum CoQ10 levels.

1. Introduction

Perturbation in the antioxidants and oxidants equilibrium results in a phenomenon called oxidative stress which is recently suggested as a contributing mechanism to epilepsy (Sudha, Rao, & Rao, 2001). The association between the generation of free radicals and their scavengers by antioxidant systems has been established in epilepsy. An increase in the formation of reactive oxygen species (ROS) has been viewed in an animal model of epilepsy as well as in neurodegeneration observed in epileptic humans (Militão, Ferreira, & de Freitas, 2010). Recent evidence shows that pro-oxidant/antioxidant imbalance can also increase the probability of seizure recurrence (Ercegovac et al., 2013). Besides, elevation in ROS production may prolong seizures duration and the development of subsequent epilepsy (Martinc, Grabnar, & Vovk, 2012; Méndez-Armenta, Nava-Ruiz, Juárez-Rebollar, Rodríguez-Martínez, & Yescas Gómez, 2014).

Coenzyme Q10 (known as coenzyme Q, ubiquinone, and ubiquinol) is a lipophilic compound mainly located in mitochondrial membranes of all tissue cells and acts as a crucial enzyme cofactor in the mitochondrial respiratory chain for the synthesis of Adenosine Triphosphate (ATP) (Matthews, Yang, Browne, Baik, & Beal, 1998). It also plays an important role as a potent antioxidant either directly by scavenging the free radicals or indirectly by regenerating other antioxidants, such as vitamin E (Matthews et al., 1998; Sattarinezhad, Shafaroodi, Sheikhnouri, Mousavi, & Moezi, 2014).

Since disturbance in the activity of antioxidative defense mechanisms may be accounted for the pathogenesis of epilepsy, and CoQ10 functions as a strong endogenous antioxidant, it is imperative to unravel the effects of CoQ10 in epileptic patients. While in vivo studies have shown the detrimental effect of CoQ10 insufficiency in epilepsy (de Sales Santos et al., 2010; Tawfik, 2011), no human studies have addressed this issue. Therefore, the first aim of the present study was to quantify the serum concentration of CoQ10, and the second aim was to figure out the clinical relevance of the type, frequency, and duration of seizures with CoQ10 levels.

2. Methods

2.1. Study population

This analytical cross-sectional study was performed in the Long Term Monitoring (LTM) Ward of the Loghman Hakim Hospital, Tehran, Iran. Medical Ethics Committee of Shahid Beheshti University of Medical Sciences approved the study (Ethics Committee number: IR.SBMU.RETECH.REC.1396.411). All subjects agreed and completed the written informed consent.

The case group included patients who were admitted to the LTM ward of Loghman Hakim Hospital due to repeated epileptic seizures. Their demographic and seizure characteristics such as type, frequency, duration, and repetition as well as the history of epileptic medications were collected through an interview with the patients. All patients underwent at least 48 hours of continuous scalp EEG monitoring to capture enough habitual seizures. The epilepsy type was confirmed by an epileptologist based

on ictal and interictal EEG findings and the semiology of the seizures. The patients with any other medical, neurological, psychiatric disorders, and history of recent head trauma were excluded from the study. The control group consisted of age and gender-matched healthy volunteers with no history of seizure. Either patients or controls were not included in the study if they received antioxidant medications such as vitamin C, corticosteroids, and non-steroidal anti-inflammatory drugs within the past month.

2.2. Blood collection and measurement of Coenzyme Q10 levels

Venous blood samples were taken from all patients within 24 hours of a habitual seizure. Five milliliters of venous blood was collected from each study participant and centrifuged at $4000 \times g$ for 10 minutes (at $4^{\circ}C$). Then serum was immediately separated and aliquots were stored at $-80^{\circ}C$.

Serum CoQ10 levels were measured using the commercially available ELISA (enzyme-linked immunosorbent assay) kit, according to the manufacturer's instructions (ZB-13164S-H9648; ZellBio GmbH, Ulm, Germany). The serum CoQ10 levels were expressed as ng/mL. The intra-assay and inter-assay coefficients of variation were 10% and 12%, respectively.

2.3. Statistical analysis

We used the mean difference and 95% confidence interval for the absolute difference of CoQ10 level (ng/mL) in the study groups. To support the normality of distribution, the Kolmogorov-Smirnov test was used. Continuous and categorical data were reported by mean \pm standard deviation and number (percentage), respectively. The independent sample t-test and Chi-square tests were applied to compare quantitative and categorical variables between the study groups. One-way Analysis of Variance (ANOVA) was used to assess the level of CoQ10 in different types of epilepsy. Furthermore, multiple linear regression analysis was performed to explore the association between CoQ10 and epilepsy characteristics (duration, frequency, and type of seizure). Statistical analysis was performed using SPSS version 16.0 (SPSS, Inc., Chicago, IL, USA). The statistical significance level was considered as $P < 0.05$.

3. Results

Demographic and clinical data for the study subjects are presented in Table 1. A total of 39 patients with Epileptic Seizures (ES), 22 men and 17 women with a mean age of 29.79 ± 11.89 years were included in the study. The control group consisted of 35 healthy volunteers, 13 men and 22 women with a mean age of 26.97 ± 6.62 years. There was no significant difference between the age and gender of the two groups.

Table 1. Demographic and clinical characteristics of subjects in the study groups

Variables	No. (%) / Mean \pm SD		P	
	Case Group (n=39)	Comparison Group (n=35)		
Sex	Male	22 (56.4)	13 (43.6)	0.11
	Female	17 (37.1)	22 (62.9)	
Age	29.7 ± 11.89	26.97 ± 6.62		0.22
Epilepsy duration (years)	13.51 ± 11.44	NA*		-
Seizure frequency (month)	11.92 ± 21.21	NA		-
Type of epilepsy	Focal onset	28 (71.8)	NA	-
	Generalized onset	11 (28.2)	NA	-
Anti-epileptic drugs used	Monotherapy	9 (23.1)	NA	-
	Polytherapy	30 (76.9)	NA	-
Serum CoQ10 (ng/ml)	11.99 ± 5.93	16.48 ± 4.20		<0.001

*Not applicable.

Table 2. Association between serum level of CoQ10 and demographic characteristics of study subjects in multiple linear regression model ($R^2=0.42$)

Variables		Mean±SD	Crude		Adjusted	
		Serum Level of CoQ10	β Coefficient	P	β Coefficient	P
Age	-	-	-0.11	0.09	-0.079	0.210
Sex	Male (reference)	13.60±5.73	0.97	0.46	0.114	0.927
	Female	14.57±5.5				
Group	Epileptic seizure(reference)	11.99±5.93	4.49	<0.001	4.243	0.001
	Healthy	16.48±4.20				

NEURSCIENCE

Table 1 presents the serum concentration of CoQ10 in ES patients compared to healthy subjects. Our finding revealed that the ES patients had a significantly lower level of CoQ10 compared to the control group ($P<0.001$).

The association of the study group, age, and sex with a serum level of CoQ10 was examined. There was a statistically significant positive association between the study group and level of CoQ10 in both crud (β : 4.49, $P<0.001$) and adjusted (β : 4.24, $P<0.001$) models. As shown in Table 2, the healthy group showed a 4.24 ng/mL increase in CoQ10 concentration when they were adjusted for age and sex covariates. It means that the observed positive significant association between study groups and serum level of CoQ10 was not attenuated after adjusting for age and sex of study subjects (Table 2).

We also measured the association of seizure type (generalized seizures versus focal seizures) with serum concentration of CoQ10. Among the 39 recorded ES episodes, 28 attacks (71.8%) were focal seizures and 11 attacks (28.2%) were generalized convulsive seizures. No statistically significant correlation was found between the type of seizure and serum CoQ10 level.

Regarding the clinical features of epilepsy, we assessed the relationship between serum levels of CoQ10 and the frequency and duration of seizures using the Pearson correlation test. The mean seizure frequency was 11.92 ± 21.21 attacks per month, and the epilepsy duration was 13.51 ± 11.44 years. Interestingly, our results showed a negative significant correlation between duration of epilepsy and serum levels of CoQ10 ($r = -0.37$, $P = 0.02$). A similar result was also detected when the correlation was examined between seizure frequency and levels of CoQ10 ($r = -0.36$, $P = 0.02$).

4. Discussion

Oxidative stress triggered by diminished endogenous antioxidants or enhanced oxidants formation is currently considered as a possible mechanism underlying epileptic seizures (Martinc, Grabnar, & Vovk, 2014). CoQ10 is a strong antioxidant that protects cells from oxidative damage through inhibiting certain enzymes involved in the formation of ROS and generating other antioxidants (El-ghoroury et al., 2009; Bhardwaj, & Kumar, 2016). However, the impact of CoQ10 on seizure characteristics in ES patients is not clear. In this study, we provide novel insights into the role of CoQ10 insufficiency in the pathophysiology of epileptic seizures. We demonstrate, for the first time, that serum concentration of CoQ10 decreases in ES patients. Our findings show that increasing the deficiency of CoQ10 results in more frequent and longer-lasting epilepsy.

It seems that the endogenous antioxidants and their repair capacity, which normally overcome the increased production of oxidants in cells, is reduced in ES patients. We thus assessed the serum levels of CoQ10, as an endogenous antioxidant, in these patients. Although baseline levels of CoQ10 could not be measured in the ES patients in our study, we found that their serum concentrations of CoQ10 were significantly lower than the control group. Decreased CoQ10 levels have also been shown to associate with various neurological diseases, including cerebral infarction, neurodegenerative processes, cerebral ataxia, and many other brain disorders (Lamperti et al., 2003, Spindler, Beal, & Henchcliffe, 2009; Ramezani, Sahraei, Simani, Heydari, & Shahidi, 2020; Simani, et al., 2018). CoQ10 deficiency could result in the enhancement of electrons transport to oxygen, which leads to the significant generation of superoxide anion (O_2^-) in mitochondria (Chew, & Watts, 2004). It

then may damage the cellular components due to the elevation of ROS and reduction in ATP production; however, the effect of insufficient CoQ10 in the former is more prominent in the pathogenesis of the diseases (Lalkovičová and Danielisová 2016; Milanlioglu et al., 2016). On the other hand, an increase in free radicals and a decrease in antioxidant level has been observed in the development of epilepsy (Cengiz, Yüksel, & Seven, 2000; Verrotti et al., 2002). Therefore, it is unclear what might underlie the decline of antioxidants such as serum CoQ10. Taken together, it can be postulated that an attenuated level of CoQ10 leads to a significant rise in ROS production, resulting in oxidative stress and thus neuronal damage in an epileptic brain.

To determine the potential role of CoQ10 in the type of seizures, we measured the correlation between these two variables. Based on our data, CoQ10 levels were not different in seizure types. This suggests that the type of epilepsy is unlikely to affect the serum concentration of CoQ10 in different ways. This finding is consistent with prior work showing no correlation between the activity of antioxidant enzymes or oxidative stress and types of seizures (Yiş, Seçkin, Kuralay, & Dirik, 2009).

This study provides clear evidence on a correlation between serum levels of CoQ10 and seizure frequency and duration of epilepsy. This issue may be related to free radical-mediated damage or a decrease in the activity of antioxidants caused by the deficiency of CoQ10 in ES patients (Cengiz et al., 2000; Verrotti et al., 2002). It has been shown that the risk of seizure recurrence increases with CoQ10 deficiency (Yiş et al., 2009). An absolute or relative deficiency in CoQ10 results in a remarkable increase in the transfer of electrons to molecular oxygen in mitochondria, leading to the overproduction of superoxide free radicals (Chew & Watts, 2004). The detrimental role of free radicals in seizures has been reported in rodent studies showing that antioxidants can reduce the oxidative stress markers in epileptic animals, accompanied by the decrease of their seizure manifestations (Tan, Manchester, Reiter, Kim, & El-Sokkary, 1998; Gupta, Briyal, & Chaudhary, 2002; Mohanan, & Yamamoto 2002; Barros et al., 2007; Xavier et al., 2007).

Furthermore, the activity of CoQ10, as an antioxidant scavenger, inhibits lipid peroxidation (Mancuso, Orsucci, Volpi, Calsolaro, & Siciliano, 2010). In this regard, findings from animal seizure models show that treatment of epileptic rats with CoQ10 exerts the neuroprotective effects by the removal of free radicals and reduction in lipid peroxidation levels and nitrite content, leading to ameliorate seizure severity (de Sales Santos et

al., 2010; Tawfik, 2011). It has also been demonstrated that pretreatment with CoQ10 during the acute phase of pilocarpine-induced seizures results in lipid peroxidation reduction and antioxidant factors elevation, leading to an overall decrease in oxidative stress (Santos et al., 2009).

Therefore, based on our results, the negative association between seizure frequency and duration of epilepsy with CoQ10 may be related to free radical-mediated damage triggered by a deficiency in CoQ10.

In conclusion, our study demonstrated significantly decreased levels of CoQ10 in ES patients. We also found that deficiency of CoQ10 would dramatically exacerbate the clinical features of epilepsy. These results suggest the development of novel methods of therapy, possibly including adjunctive antioxidant treatment. However, the study should be replicated in a larger sample of subjects.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Medical Ethics Committee of Shahid Beheshti University of Medical Sciences (Core: IR.SBMU.RETECH.REC.1396.411). Written informed consent was obtained from all the participants.

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Authors' contributions

Conceptualization, investigation, and writing – original draft: Leila Simani and Omidvar Rezaei; Data collection: Fari Ryan, Masoumeh Sadeghi, Etrat Hooshmandi, and Mahtab Ramezani; Data analysis, Writing–review & editing: Leila Simani, Fari Ryan, Masoumeh Sadeghi, and Hossin Pakdaman.

Conflict of interest

The authors declared no conflict of interest.

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