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CLINICAL TRIAL STUDY

Coenzyme Q10 in the Treatment of Attention Deficit Hyperactivity Disorder in Children: A Randomized Controlled Trial

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Abstract: ***Background*:** Attention Deficit Hyperactivity Disorder is a common child neurobehavioral disorder whose pathogenesis is not completely understood. However, some evidence indicates a crucial link between this disorder and the degree of oxidative stress. Coenzyme Q10 (ubiquinol) is an antioxidant that may play a significant role in the treatment of Attention Deficit Hyperactivity Disorder.

***Objective*:** To assess the safety and efficacy of coenzyme Q10 as an add-on drug treatment for attention deficit hyperactivity disorder.

***Method*:** Sixty children, aged 6-16 years, with attention deficit hyperactivity disorder, non-responders to atomoxetine treatment for 6 months, were included in this double-blind, randomized, and controlled study. Group 1 received atomoxetine plus coenzyme Q10, and group 2 received atomoxetine plus placebo for 6 months. Follow-up by CONNERS parent rating scale questionnaire (CPRS-48) was performed before and after 1, 3, and 6 months of treatment, and any drug-related side effects were reported.

***Results*:** The addition of coenzyme Q10 to atomoxetine in group 1 improved symptoms in a shorter time with minimal adverse effects. Group 1 showed improvement of about 33.87% in CPRS-48 total score versus 18.24% in group 2. There was a statistically significant decrease in CPRS-48 total score and its three subscales (learning problems, impulsive hyperactive subscale, and 10-items hyperactivity index) in group 1 versus group 2 after six months of treatment (p-value <0.001).

***Conclusion*:** Coenzyme Q10 has an important role as an add-on drug treatment for attention deficit hyperactivity disorder by improving symptoms, particularly hyperactivity, and in minimizing atomoxetine adverse effects.

***Trial Registration*:** The study was registered at clinicalTrials.gov (https://clinicaltrials.gov/). Registration identification number: NCT04216186.

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1. INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a complex, chronic developmental disorder with typical onset in early childhood and known persistence throughout adolescence and adulthood [1].

The condition may cause significant psychosocial impairment in academic performance, work satisfaction, and social interactions. DSM-V divided its symptoms into two categories (inattention and hyperactivity/impulsivity) that include behaviors like failure to pay close attention to details, difficulty organizing tasks and activities, excessive talking, fidgeting, or an inability to remain seated in appropriate situations [2].

Estimates of the prevalence of ADHD vary worldwide. The American Psychiatric Association estimated that 5% of children have ADHD. There are some gender differences to consider when diagnosing ADHD, with more males being diagnosed than females (ratio 2:1). A higher prevalence of ADHD (7.47%) is present in children and adolescents in Africa [1, 2].

Pharmacological therapy remains the mainstay of treatment for patients diagnosed to have ADHD. It is divided into two major categories, which fall into stimulants or non-stimulants. Atomoxetine is a non-stimulant substance with a Federal Drug Administration (FDA) prescription for ADHD control in children over 6 years of age, teenagers and adults [3].

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Stimulant medications are effective for up to 80% of ADHD patients, but a portion of patients do not respond or cannot tolerate its known side effects. For the treatment of this condition, atomoxetine provides an alternative remedy [4].

Many parents, however, prefer not to use these pharmacotherapies to manage ADHD. Alternative and complementary agents such as natural supplements are used to treat ADHD instead [5].

The brain is particularly susceptible to oxidative stress due to its high lipid content. Neurons have an especially high need for energy consumption. Neurons use mitochondria to produce adenosine triphosphate (ATP) to power the ion pumps concentrated in the pre-synaptic terminals and needed to restore the membrane potentials after depolarization and neurotransmitter release [6].

During ATP production, partial reduction of oxygen produces harmful "side products" like superoxide anion. Therefore, the increased energy demand by neurons and synapses further aggravates the risk of oxidative stress for brain disorders like ADHD. The increased ratio of oxidative to antioxidative status in ADHD indicates the possibility that ADHD people cannot mount a sufficient response to increased oxidative stress [7].

Data regarding the relationship of ADHD with oxidant-antioxidant imbalances offers possibilities to use antioxidant therapy in ADHD. So, dietary antioxidantsare recently used in ADHD management [8].

Coenzyme Q10 is essential for the cell power supply in mitochondria. It shuttles electrons from complexes I and II to complex III and can be anti-oxidative. Coenzyme Q10 supplementation has been frequently used to treat many neurological disorders [9].

This study was designed to assess the safety and efficacy of coenzyme Q10 as an add-on drug treatment for ADHD.

2. METHODS

This randomized study was carried out at the Pediatrics Department of Kafr-Elsheikh University Hospital (January 2019 to October 2020) on sixty children aged 6 - 16 years who suffered from ADHD. This study was conducted according to the Declaration of Helsinki principles. Our institutional ethical committee approval was obtained, and written consent was taken from the guardians of each child. They were also informed of any possible side effects of drugs. The study was registered at clinicalTrials.gov (https://clinicaltrials.gov/). Registration identification number was NCT04216186.

The study included children with ADHD who were non-responders to atomoxetine for 6 months and were diagnosed by the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-V) criteria [10], and the score was given by CPRS-48 [11]. Participants were defined as non-responders to atomoxetine treatment if they received atomoxetine for 6 months and their total scores of CPRS-48 stayed ≥ 50.

The study included children aged between 6 and 18 years. Patients with other comorbidities like autism, anxiety, or obsessive-compulsive disorder were excluded from this study. In addition, the patient's unwillingness to participate in the trial and the existence of any atomoxetine contraindications were considered exclusions from the study.All children meeting the inclusion criteria were randomly assigned into one of the two groups:

Group1 (study group) included 30 children who received treatment in the form of atomoxetine in a dose of 0.5-1.8 mg/kg/day plus coenzyme Q10 in a dose of 1-3 mg/kg/dose [12, 13].

Group 2 (control group) included 30 children who received treatment in the form of atomoxetine in a similar dose plus placebo.

All patients were applied to CPRS-48 [11], which is a revised 48-item version created from the 93-item version. The changes included slight rewording and substantial shortening to simplify administration and interpretation. We assessed our primary outcome using this shorter rating form, which provides a qualitative and quantitative picture of children's emotions and behavior [14].

This questionnaire was performed before and after 1, 3, and 6 months of treatment (Fig. **1**).

Randomization and Masking: The random number list was generated by computer software. Allocation concealment was performed by sequentially numbered sealed opaque envelopes. Once the written consent was signed, the sealed opaque envelope was opened, and the child was enrolled into the respective group by the doctor on duty who was not blinded and not a part of the study. All other treating staff and outcome assessors were blinded to the treatment group.

Statistical analysis: Data was fed to the computer and analyzed using IBM SPSS software version 20.0 (Armonk, NY: IBM Corp). Qualitative data were described using numbers and percentages. The Kolmogorov-Smirnov test was used to verify the normality of distribution. Quantitative data were described using range (minimum and maximum), mean, standard deviation, median, and IQR. The significance of the obtained results was judged at the 5% level. The type of the sample was accessibility (convenient) sample which included all the patients who visited the outpatient clinic during the period of the study.

The used tests were: 1. Chi-square test (For categorical variables, to compare between different groups).

2. Student t-test (For normally distributed quantitative variables, to compare between two studied groups).

3. Monte Carlo correction (Correction for chi-square when more than 20% of the cells have expected count less than 5).

4. Mann Whitney test (For abnormally distributed quantitative variables, to compare between two studied groups).

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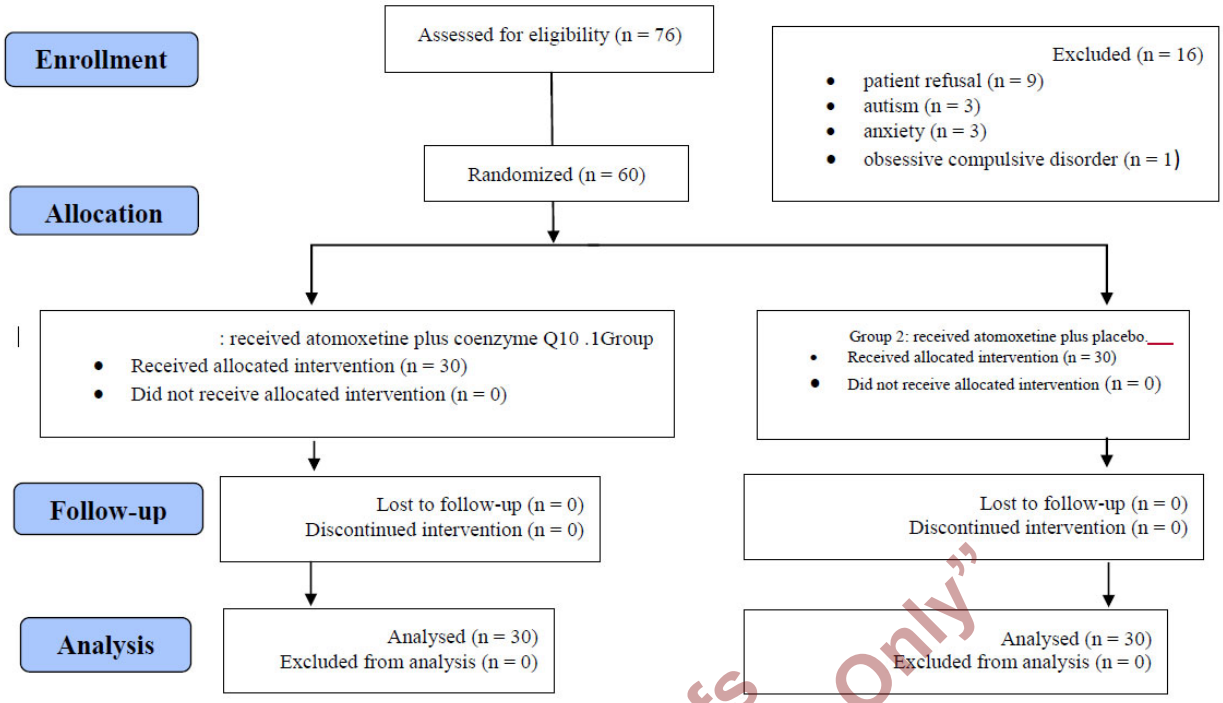


Fig. (1). Information flow chart regarding the study (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

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Availability of Data and Materials: The protocol and data supporting the findings of the article are available through direct contact with the corresponding author, beginning at 12 months and ending at 24 months following article publication.

3.. RESULTS

Sixty children (40 boys and 20 girls) were included in this study. Group 1 included 30 patients (11 females and 19 males) with mean age (8.68 ± 2.73) years. Meanwhile, group 2 included 30 patients (9 females and 21 males) with mean age (8.42 ± 2.59) years (Fig. **1**).

There was no statistically significant difference between the two studied groups' pretreatment regarding total CPRS-48 score and its three subscales (learning problems, impulsive hyperactive subscale, and 10-items hyperactivity index) (Table **1**).

There was no statistically significant difference between the two studied groups after one month of treatment regarding the total CPRS-48 score and learning problems subscale. However, there was a high statistically significant decrease in impulsive hyperactive subscale and 10-items hyperactivity index subscale in group 1 versus group 2 after one month of treatment (p-value = 0.004 and 0.001, respectively) (Table **2**).

There was no statistically significant difference between the two studied groups after three months of treatment regarding total CPRS-48 score. But, there was a statistically significant decrease in the learning problems subscale in group 1 versus group 2 after three months of treatment (p-value = 0.047). Also, there was a highly statistically significant decrease in impulsive hyperactive subscale and 10-items hyperactivity index subscale in group 1 versus group 2 after three months of treatment (p-value < 0.001) (Table **3**).

Moreover, there was a statistically significant decrease in the total CPRS-48 score and its three subscales (learning problems, impulsive hyperactive subscale, and 10-items hyperactivity index) in group 1 versus group 2 after six months of treatment (p-value < 0.001) (Table **4**).

The percentage of improvement of total CPRS-48 score after 6 months of therapy was about 33.87%in group 1 versus 18.24% in group 2. The percentage of improvement of learning problems after 6 months of therapy was about 41.81% in group 1 versus 22.72% in group 2. The percentage of improvement of impulsive hyperactivity subscale after 6 months of therapy was about 44.03% in group 1 versus 21.23% in group 2. The percentage of improvement of hyperactivity index after 6 months of therapy was about 37.05% in group 1 versus 14.82% in group 2 (Table **5**).

In terms of adverse effects, five children in group 1 developed nausea. While six children in group 2 developed abdominal pain and three children lost weight (Table **6**).

Table 1. Comparison between the two groups according to total CONNERS score and its subscales (Pretreatment).

-	Group1 (n = 30)		Group 2 (n = 30)		T	P
	Min - Max	Mean ± SD	Min - Max	Mean ± SD		
Total CONNERS	50.0 - 82.0	68.70 ± 10.13	50.0 - 79.0	67.03 ± 8.05	0.706	0.483
Learning problems	7.0 - 12.0	9.73 ± 1.64	6.0 - 12.0	9.17 ± 1.56	1.374	0.175
Impulsive hyperactive subscale	6.0 - 11.0	8.63 ± 1.27	6.0 - 11.0	8.80 ± 1.40	0.483	0.631
10 - items Hyper activity index	15.0 - 22.0	18.43 ± 1.83	16.0 - 23.0	18.70 ± 1.88	0.557	0.58

*SD: Standard Deviation; Min: Minimum; Max: Maximum; t: Student t-test; U: Mann Whitney test; m: months; n: number

Table 2. Comparison between the two groups according to total CONNERS score and its subscales (After 1month).

-	Group1 (n = 30)		Group 2 (n = 30)		T	P
	Min - Max	Mean ± SD	Min - Max	Mean ± SD		
Total CONNERS	40.0 - 80.0	60.77 ± 10.0	80.0 - 83.0	63.80 ± 9.01	1.234	0.222
Learning problems	5.0 - 12.0	8.17 ± 1.80	5.0 - 11.0	8.17 ± 1.49	0	1
Impulsive hyperactive subscale	3.0 - 11.0	6.80 ± 1.71	5.0 - 11.0	7.97 ± 1.30	2.975	0.004*
10 - items Hyper activity index	12.0 - 20.0	15.87 ± 2.16	14.0 - 24.0	17.90 ± 2.20	3.609	0.001*

SD: Standard Deviation; Min: Minimum; Max: Maximum; t: Student t-test; U: Mann Whitney test; m: months; n: number; *Significant at $p \leq 0.05$.

Table 3. Comparison between the two groups according to total CONNERS score and its subscales (After 3 months).

-	Group1 (n = 30)		Group 2 (n = 30)		T	P
	Min - Max	Mean ± SD	Min - Max	Mean ± SD		
Total CONNERS	37.0 - 70.0	51.47 ± 8.40	40.0 - 79.0	57.37 ± 10.46	2.409	0.019*
Learning problems	4.0 - 10.0	6.90 ± 1.52	5.0 - 11.0	7.73 ± 1.66	2.030	0.047*
Impulsive hyperactive subscale	3.0 - 10.0	5.67 ± 1.79	4.0 - 10.0	7.33 ± 1.63	3.778	<0.001*
10 - items Hyper activity index	9.0 - 20.0	13.60 ± 2.46	12.0 - 21.0	16.50 ± 2.11	4.900	<0.001*

SD: Standard Deviation; Min: Minimum; Max: Maximum; t: Student t-test; U: Mann Whitney test; m: months; n: number; *Significant at $p \leq 0.05$.

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Table 4. Comparison between the two groups according to total CONNERS score and its subscales (After 6 months).

-	Group1 (n = 30)		Group 2 (n = 30)		T	P
-	Min - Max	Mean ± SD	Min - Max	Mean ± SD		
Total CONNERS	33.0 - 60.0	45.23 ± 7.44	38.0 - 71.0	54.93 ± 9.75	4.333	<0.001*
Learning problems	3.0 - 9.0	5.70 ± 1.51	5.0 - 9.0	7.03 ± 1.35	3.601	0.001*
Impulsive hyperactive subscale	1.0 - 8.0	4.87 ± 1.59	5.0 - 9.0	6.87 ± 1.28	5.364	<0.001*
10 - items Hyper activity index	8.0 - 18.0	11.60 ± 2.62	13.0 - 21.0	15.90 ± 2.02	7.113	<0.001*

SD: Standard Deviation; Min: Minimum; Max: Maximum; t: Student t-test; U: Mann Whitney test; m: months; n: number; *Significant at $p \leq 0.05$.

Table 5. Percent of improvement in the the two groups.

-	Group1 (n = 30)	Group 2 (n = 30)	U	P
Total CONNERS	↓33.87 ± 7.65%	↓18.24 ± 8.90%	U=84.0	<0.001*
Learning problems	↓41.81 ± 10.84%	↓22.72 ± 11.48%	U=106.0	<0.001*
Impulsive hyperactive subscale	↓44.03 ± 16.20%	↓21.23 ± 13.87%	U=114.50	<0.001*
10 - items Hyper activity index	↓37.05 ± 12.41%	↓14.82 ± 8.19%	U=66.0	<0.001*

U: Mann Whitney test; n: number; *Significant at $p \leq 0.05$.

Table 6. Comparison between the two studied groups according to side effect.

Side Effect	Cases (n = 30)		Control (n = 30)		χ^2	^{MC}p
	No.	%	No.	%		
No side effects	25	83.3	19	63.3	5.804	0.052
Git symptoms	5	16.7	6	20.0		
Weight loss	0	0.0	5	16.7		

χ^2: Chi square test; ^{MC}p: Monte Carlo

4. DISCUSSION

Data regarding the relationship of ADHD with oxidant-antioxidant imbalances offers possibilities to use antioxidant therapy in ADHD. So, dietary antioxidant was recently used in ADHD management [8]. This study was designed to assess the safety and efficacy of coenzyme Q10 as an add-on drug treatment for ADHD.

ADHD can be treated with different types of medication. In 2003, non-stimulants were approved for the treatment of ADHD. Drugs can affect children differently as one child can respond to one medication well, but not to another [15]. It is worth mentioning that this drug is widely available in our country in contrast to stimulants. This is the rationale behind its wide use in our region.

At least 30% of children affected do not respond adequately to a single drug trial or cannot tolerate it [16]. Data on all ADHD medications are limited on both long-term effectiveness and long-term adverse effects. Studies for their use in preschool age groups are also limited [17].

So, the need for alternative and complementary treatments of ADHD with few adverse effects is crucial nowadays, with the increasing prevalence of children suffering from it worldwide. The use of antioxidants against oxidative conditions in the treatment of several neuropsychiatric disorders is an emerging field [18].

Preliminary assessments of appropriate antioxidants and dietary supplements showed improvement and regression of oxidative stress in the affected brain [18].

Coenzyme Q10 has an antioxidant role [8]; so, it could be promising in the treatment of many neuropsychiatric disorders like ADHD.

There is no sufficient data from previous studies about the combined use of atomoxteine and coenzyme Q10 in treating ADHD. Besides, the role of coenzyme Q10 in the treatment of autism has been well studied [19-23].

In this study, the two groups showed improvement in symptoms of ADHD after 6 months of treatment, but the addition of coenzyme Q10 to atomoxetine in group I showed superior results regarding CPRS-48 total score and its three subscales (learning problems, impulsive-hyperactive, and hyperactivity index). Group 1 showed an improvement of about 33.87% in total CPRS-48 score versus 18.24% in group 2.

Although some improvement in symptoms can be achieved in a patient as early as one week after the start of atomoxetine treatment alone, however, full effect usually takes longer time. In randomized trials, the median time of change in ADHD symptoms was 3.7 weeks. Evidence from these studies suggests that the likelihood of symptom improvement may continue to increase until 52 weeks after initiation of the treatment [22].

The addition of coenzyme Q10 to atomoxetine in this study provided more improvement in symptoms in a shorter time. Improvement in hyperactivity index was significant after 1 month of therapy, and its percentage of improvement after 6 months was 37.05% in group 1 versus 14.82% in group 2. Therefore it can be concluded that atomoxetine partial responders can benefit from the addition of coenzyme Q10.

To the best of our knowledge, this is the first randomized trial to assess the role of coenzyme Q10 as an add-on drug treatment for attention deficit hyperactivity disorder.

The most common side effects reported with atomoxetine use in clinical trials were reduced appetite and weight loss early during treatment [23]. In our study, it was obvious that the frequency of these common adverse events was less reported. This may be attributed to the use of coenzyme Q10 in treatment.

That was in agreement with Gvozdjáková *et al.* [19], who demonstrated that supportive treatment with coenzyme Q10 showed improvement of symptoms in children with autism, as contact with parents (in 12%), verbal communication (in 21%), playing games of children (in 42%), sleep (in 34%), and refusal of food (in 17%). The favorable effect of ubiquinol has been shown in children with autism [19]. In autism spectrum disorder, coenzyme Q10 serum level was significantly decreased in comparison to healthy children.

The main limitation of the study was the short duration of follow-up. So, further studies with a longer duration of follow-up are needed to document these findings.

CONCLUSION

Coenzyme Q10 has an important role as an add-on drug in the treatment of ADHD by improving symptoms, particularly (hyperactivity) and minimizing atomoxetine adverse effects.

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TRIAL STATUS

The study was registered at https://clinicaltrials.gov/ with trial number identifier: NCT04216186.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The research was approved by the Institutional ethical committee of Kafr-Elsheikh University, with approval number: 1/605/23118.

HUMAN AND ANIMAL RIGHTS

No animals were used in this study. The study on humans was conducted in accordance with the ethical rules of the Helsinki Declaration.

CONSENT FOR PUBLICATION

Written consent was taken from the guardians of the children, and they were also informed of any possible side effects of drugs.

STANDARD OF REPORTING

Consort guidelines were followed in this study.

AVAILABILITY OF DATA AND MATERIALS

The protocol and data supporting the findings of the article are available through direct contact with the corresponding author, beginning at 12 months and ending at 24 months following article publication.

FUNDING

Declared none.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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