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SYSTEMATIC REVIEW

Mitochondrial Enhancement for Neurodegenerative Movement Disorders: A Systematic Review of Trials Involving Creatine, Coenzyme Q10, Idebenone and Mitoquinone

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Abstract
Background Neurodegenerative movement disorders mainly include Parkinson's disease (PD), atypical parkinsonisms, Huntington's disease (HD), and Friedreich's ataxia (FA). With mitochondrial dysfunction observed in these diseases, mitochondrial enhancement such as creatine, coenzyme Q10 (CoQ10) and its analogues (idebenone and mitoquinone) has been regarded as a potential treatment.
Aim In this paper, we systematically analysed and summarized the efficacy of mitochondrial enhancement in improving motor and other symptoms in neurodegenerative movement disorders.
Methods We searched the electronic databases PubMed, EMBASE, CINAHL, Cochrane Library and China National Knowledge Infrastructure until September 2013 for eligible randomized controlled trials (RCTs), as well as unpublished and ongoing trials. We calculated the mean differences for continuous data with 95 % confidence intervals and pooled the results using a fixed-effect model, if no significant statistical heterogeneity was found ($I^2 < 50$ %).
Results We included 16 studies with 1,557 randomized patients, which compared creatine, CoQ10 or its analogues with placebo in motor and other symptoms. No significant improvements were found in the motor symptoms of PD, atypical parkinsonisms or HD patients, while only the high dose of idebenone seems to be promising for motor improvement in FA. Certain benefits are found in other symptoms.
Conclusions There is insufficient evidence to support the use of mitochondrial enhancement in patients with neurodegenerative movement disorders. More well-designed RCTs with large samples are required for further confirmation.

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1 Introduction

Neurodegenerative diseases (NDs) are generally acknowledged as a group of neurological disorders with degeneration and loss of neurons, and most are with pathological accumulations in the brain. Clinical movement disorders are the main symptoms in some NDs, such as Parkinson's disease (PD), atypical parkinsonisms, Huntington's disease (HD), and Friedreich's ataxia (FA). Meanwhile, non-motor symptoms are also common in the course of NDs. Although neurodegeneration is one of the most important topics in neuroscience research, and huge resources have been devoted into this field, there is still a lack of efficient methods to completely prevent the progression of these diseases. The current aim in clinical therapy is mainly focused on relieving symptoms and life quality improvement.

Mitochondrial dysfunction has been suggested to be involved in the pathophysiological process of NDs. Creatine, coenzyme Q10 (CoQ10) and its analogues, idebenone and mitoquinone (or MitoQ), are believed to complement energy by improving mitochondrial function. Therefore, they were regarded as potential neuroprotective agents for NDs [1]. Moreover, it has been found that both CoQ10 and creatine can inhibit the loss of nigral dopaminergic neurons in animal PD models [2, 3]. The incidence of 'PD has been found to correlate with the enzyme NADH-quinone oxidoreductase (NQO1) genotype frequencies [4]. NQO1 was proved to be crucially involved in pharmacologically important

benzoquinone redox-shuttling in the cellular environment [5]. Gene COQ2 is in charge of encoding para-hydroxybenzoate polyprenyltransferase, which is important for the biosynthesis of CoQ10. A recent study demonstrated the impaired gene COQ2 is closely associated with multiple system atrophy (MSA), a type of atypical parkinsonism [6].

So far, some randomized controlled trials (RCTs) have already been conducted which focused on mitochondrial enhancement such as creatine, CoQ10 and its analogues in comparison with placebo for the treatment of cardiovascular diseases, mitochondrial disorders and NDs with well tolerance. Certain benefits have been found, especially with idebenone, for the treatment of FA [7]. Hereby, we systematically analysed and summarized the efficacy of mitochondrial enhancement in improving motor and other symptoms in neurodegenerative movement disorders.

2 Methods

We searched the electronic databases PubMed, EMBASE, CINAHL, Cochrane Library and China National Knowledge Infrastructure (CNKI) until September 2013 for all possible trials. For unpublished and ongoing trials, we searched the US National Institute of Health clinical trial site (http://www.clinicaltrials.gov/) and the WHO International Clinical Trials Registry Platform (http://www.who.int/ictrp/en/). We also used Science Citation Index Cited Reference Search for forward tracking of important articles, as well as reference lists of relevant reviews and retrieved articles. The key search terms included: (creatine OR CoQ10 OR Idebenone OR Mitoquinone) AND (Parkinson's disease OR Multiple system atrophy OR Progressive supranuclear palsy OR Corticobasal degeneration OR Dementia with Lewy bodies OR Huntington's disease OR ataxia) and their Chinese equivalents. There were no language limitations. We only included RCTs with either a parallel or crossover design. Two authors (JL, LW) independently evaluated and included the eligible trials. We calculated the mean differences (MD) for continuous data with 95 % confidence intervals (CIs) based on the same instrument. For studies with more than one experimental group, we combined all relevant experimental groups of the study into a single group. Concerning missing standard deviations for changes from baseline, we calculated these with CIs, standard errors, and *t*- or *p*-values, according to the principles provided in the Cochrane handbook [8]. We pooled the results using a fixed-effect model, if no significant statistical heterogeneity was found ($I^2 < 50$ %). When there was significant clinical heterogeneity, a descriptive summary of the results was given. We planned to use funnel plots to examine potential publication bias if more than ten trials were involved in the meta-analysis. Sensitivity analysis was undertaken where necessary.

3 Results

We identified a total of 796 references from the electronic database searches after excluding duplicates (Fig. 1). After screening of titles and abstracts, we obtained the full papers of 85 studies and assessed them for eligibility. According to the inclusion criteria, we included 16 studies with 1,557 randomized patients. Details of the included studies are provided in Table 1.

3.1 Efficacy in Motor Symptoms

As a result, seven RCTs with 802 randomized PD patients compared creatine, CoQ10 or its analogues with placebo [9–16]. An unpublished phase III trial on CoQ10 for PD compared placebo plus vitamin E (1,200 IU/day) versus CoQ10 at 1,200 mg/day plus vitamin E (1,200 IU/day) versus CoQ10 at 2,400 mg/day plus vitamin E (1,200 IU/day). No difference was seen among the groups when comparing the Unified Parkinson's Disease Rating Scale (UPDRS) outcomes, and the study was halted as it was

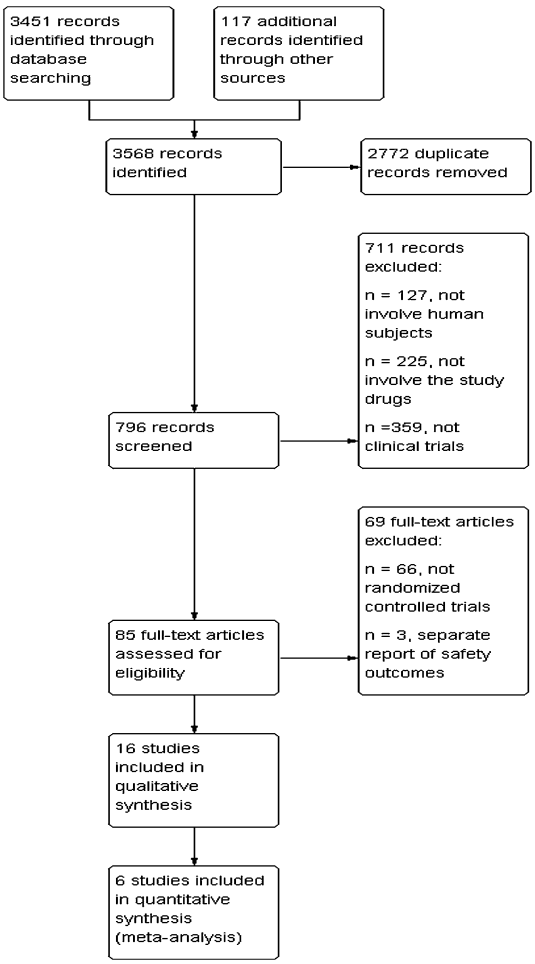

Fig. 1 Study flow diagram

Table 1 Baseline characteristics of included studies

Study	Study design	No. randomized	Subjects	Intervention	Risk of bias[a]
Bender et al. [9]	Parallel	60	Subjects with PD (Hoehn and Yahr ≤2.5)	Randomly assigned into placebo or creatine for 2 years (20 g/day for 6 days, followed by 2 g/day for 6 months and 4 g/day for the remainder)	U,U,L,L,L,L
Hass et al. [10]	Parallel	20	Subjects with PD (Hoehn and Yahr ≤3)	Randomly assigned 1:1 into placebo or creatine for 12 weeks (20 g/day for 5 days, followed by 5 g/day for the remainder)	U,U,L,L,L,L
Müller et al. [11]	Parallel	28	Subjects with PD	Supplementation coenzyme Q10 (360 mg/day) or placebo for 4 weeks	L,U,L,L,L,L
The NINDS NET-PD Investigators [12]	Parallel, multicentre	200	Age ≥30 years with early, untreated PD	Randomly assigned 1:1:1 into the minocycline group (200 mg/day), creatine group (10 g/day) or placebo group for, at most, 12 months, with an additional 6 months follow-up	U,U,L,L,L,L
The NINDS NET-PD Investigators [13]	Parallel, multicentre	213	Early untreated PD	Randomly assigned 1:1:1 into coenzyme Q10 (2,400 mg/day), GPI-1485 (4,000 mg/day) or placebo for, at most, 12 months	L,L,L,L,L,L
Shults et al. [14]	Parallel, multicentre	80	Age ≥30 years with early, untreated PD	Random assignment to placebo or coenzyme Q10 at dosages of 300, 600, or 1,200 mg/day for 16 months	L,L,L,L,L,L
Snow et al. [15]	Parallel, multicentre	130	Early untreated PD with age ≥30 years	Randomly assigned into MitoQ (40 mg/day), MitoQ (80 mg/day) or placebo over 12 months	U,U,L,L,L,L
Storch et al. [16]	Parallel, multicentre	131	Subjects with PD (Hoehn and Yahr 2–3)	Random assignment to placebo or nanoparticular coenzyme Q10 (300 mg/day) group for 3 months	L,L,L,L,L,L
Stamelou et al. [17]	Parallel	21	Clinically probable PSP, stage ≤3	Subjects were randomized in a 1:1 ratio into 5 mg/day/kg body weight of nanoparticular coenzyme Q10 or placebo for 6 weeks	L,L,L,L,L,L
Hersch et al. [18]	Parallel	64	Confirmed HD	Randomly assigned 1:1 into placebo or creatine 8 g/day for 16 weeks	L,U,L,L,L,L
The Huntington Study Group [19]	Parallel, multicentre	347	Confirmed HD	Randomly assigned into coenzyme Q10 (600 mg/day), remacemide (600 mg/day), combination or placebo for 30 months	L,U,L,L,L,L
Ranen et al. [20]	Parallel	100	Confirmed HD	Randomly assigned into idebenone (90 g/d tid) or placebo for 12 months	U,U,L,L,L,L
Di Prospero et al. [21]	Parallel	48	Confirmed FA, between 9 and 17 years	Randomly assigned 1:1:1:1 into low-dose idebenone (4–8 mg/kg), intermediate dose (10–20 mg/kg), high dose (30–50 mg/kg) or placebo for 6 months	L,L,L,L,L,L
Lynch et al. [22]	Parallel	70	Confirmed FA, between 7 and 18 years	Randomly assigned 1:1:1 into high dose idebenone, low dose idebenone or placebo for 6 months, then 68 patients continued high dose for 12 months	L,L,L,L,L,L
Mariotti et al. [23]	Parallel	29	Confirmed FA	Randomly assigned 1:1 into idebenone (5 mg/kg/day) or placebo for 1 year	L,U,L,L,L,L
Schöls et al. [24]	Crossover	16	Age 18–55 years, with gene-confirmed FA	Creatine (6.75 g/day tid), L-carnitine (3 g/day tid) and placebo were given in a randomized order in a crossover design. Each study period lasted 4 months, with washout periods of 4 weeks	U,L,L,L,L,L

L low risk, *U* unclear risk, *FA* Friedreich's ataxia, *HD* Huntington disease, *NINDS* National Institute of Neurological Disorders and Stroke, *NET-PD* Neuroprotection Exploratory Trials in PD, *PD* Parkinson's disease, *PSP* progressive supranuclear palsy, *MitoQ* Mitoquinone, *tid* three times daily

[a] Risk of bias (random sequence generation, allocation concealment, patient blind, assessor blind, dropout or withdraw, selective report)

determined to be futile to continue. For atypical parkinsonisms, one RCT with 21 randomized progressive supranuclear palsy (PSP) patients reported improvement by PSP Rating Scale compared with placebo [17]. By meta-analysis, the change of motor score in UPDRS was MD −0.54, 95 % CI −1.08–0.00, $p = 0.05$; level of heterogeneity $\chi^2 = 5.14$, degrees of freedom (df) = 5, $p = 0.40$, $I^2 = 3$ % (Fig. 2). By sensitivity analysis with random-

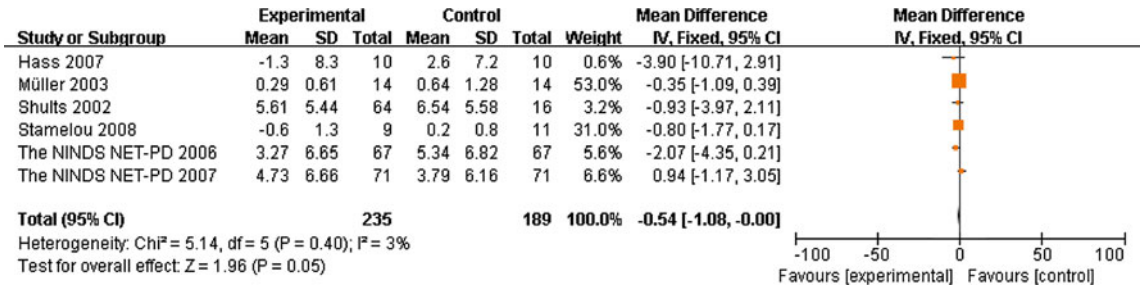

Fig. 2 Changes of UPDRS motor score after mitochondrial enhancement in Parkinson's disease and atypical parkinsonisms. As far as the changes of UPDRS motor score, no significant differences were found between mitochondrial enhancement and placebo. Creatine versus placebo for PD (Hass 2007 [10], The NINDS NET-PD 2006 [12]); CoQ10 versus placebo for PD (Müller 2003 [11], Shults 2002 [14], The NINDS NET-PD 2007 [13]); CoQ10 versus placebo for PSP (Stamelou 2008 [17]). *CoQ10* coenzyme Q10, *SD* standard deviation, *NINDS* National Institute of Neurological Disorders and Stroke, *NET-PD* Neuroprotection Exploratory Trials in PD, *PD* Parkinson's disease, *PSP* progressive supranuclear palsy, *UPDRS* Unified Parkinson's Disease Rating Scale, *df* degrees of freedom

effect model, no significance was found (MD −0.55, 95 % CI −1.11–0.02, $p = 0.06$; level of heterogeneity $\chi^2 = 5.14$, $df = 5$, $p = 0.40$, $I^2 = 3$ %). In the forest plots, the larger boxes were correlated to the smaller standard deviation and meant more weight in the result of meta-analysis. For HD, two RCTs, respectively, with CoQ10 and creatine versus placebo found no difference in the changes of motor score or chorea score in the Unified Huntington's Disease Rating Scale [18, 19], while one RCT with idebenone versus placebo found no difference in eye movement scale, chorea scale, and motor impairment scale [20]. Four RCTs on FA were measured by the International Cooperative Ataxia Rating Scale (ICARS). Three of these focused on idebenone versus placebo [21–23], and one RCT compared the efficacy between creatine and placebo [24]. No improvement of motor symptoms was found in creatine and low-dose idebenone [22–24]. However, the dose-related response of idebenone in FA was found, as well as the significant changes in ICARS in high-dose idebenone in comparison with placebo [21].

3.2 Efficacy in Other Symptoms

For PD and PSP patients, five RCTs reported changes in activities of daily living (ADL) score [10, 12–14, 17]. Significant difference was only found in the study by Shults et al. between CoQ10 and placebo for 16-month treatment in PD (MD −2.07, 95 % CI −3.72 to −0.42, $p = 0.01$) [14]. Other benefits were found, including improvements of 5 mg/day/kg nanoparticular CoQ10 for 6 weeks in PSP measured by the Frontal Assessment Battery, and cerebral energy metabolism on magnetic resonance spectroscopy [17]; improvements of 360 mg/day CoQ10 for 4 weeks in the Farnsworth-Munsell 100 Hue test in PD [11]; improvements of creatine with 20 g/day for 6 days, followed by 2 g/day for 6 months, and 4 g/day for remainder until 2 years in the UPDRS mentation, behaviour and mood in PD [9]; benefits of 600 mg/day CoQ10 for 30 months in the Brief Test of Attention and the Stroop test in HD [19]; and decrease in serum 8-hydroxy-2′-deoxyguanosine (8OHdG) by 8 g/day creatine for 16 weeks in HD, the indicator of oxidative injury to DNA [18]. Hypertrophic cardiomyopathy is the most common complication in FA patients. One RCT suggested that 5 mg/kg/day idebenone for 1 year could reduce interventricular septal thickness and left ventricular mass compared with placebo [23], while another study concluded idebenone could not decrease left ventricular hypertrophy or improve cardiac function [25].

4 Discussion

There were controversies surrounding the CoQ10 levels in PD patients. Earlier evidence from a Spanish group in 2000 did not demonstrate any statistically significant difference of CoQ10 levels in PD (with or without levodopa therapy) versus controls, even when normalizing for serum cholesterol levels [26]. Conversely, more recently a group evaluating levels of multiple nutritionally-derived antioxidants using a functional intracellular assay found that CoQ10 was more frequently functionally deficient in PD patients compared with controls [27]. So far, no evidence has suggested that ND patients were typically deficient in creatine, but poor permeability of the blood-brain barrier for creatine has been detected [28]. It is important to note that trials utilizing CoQ10 and creatine were not intended to replace patients with deficient levels, but rather to augment mitochondrial function, thereby enhancing neuronal bioenergetics. Therefore, selectively treating ND patients with deficiencies may still yield similar results.

Furthermore, no studies evaluated the efficacy of idebenone in PD or atypical parkinsonisms, although CoQ10

has been widely applied. Actually, the pharmacological differences in CoQ10 and its analogues may cause the different effects [29, 30]. Although the use of idebenone as a neuroprotective agent is a worthy idea, there was only an isolated in vitro study suggesting that idebenone induced apoptotic cell death in a commonly used cell line in the study of PD, human dopaminergic SHSY-5Y cells, which may explain why this has not been done to date [31]. Due to insufficient data, subgroup analyses focusing on the different populations of PD patients such as those with decreased complex I activity or parkin/PINK1 mutations, were not available. As far as atypical parkinsonisms are concerned, only one RCT evaluated the efficacy of CoQ10 in PSP patients, while other types such as MSA, dementia with Lewy body and corticobasal degeneration have still not been investigated in terms of any mitochondrial enhancement. In regard to positive association between the impaired gene COQ2 and MSA, CoQ10 and its analogues can be tested as potential interventions for patients with MSA in future RCTs.

Although none of the included studies reported positive findings in the UPDRS motor score, a borderline result was found from data synthesis. Therefore, we should carefully explain the negative results based on current human trials, which might be attributed to the study limitations. Duration of treatment for more than 2 years was only found in one RCT, which focused on HD. The shorter duration of trials, compared with typical duration of disease progression, might affect the effects. Moreover, it would be better to identify at-risk patients and start these treatments earlier. It is thought that the failure of these treatments may, in part, be due to difficulty reversing the considerable damage needed to cause clinically significant symptoms. The measurement of outcomes need to be more accurate. For instance, 8OHdG was thought to predict the progression of HD. However, a recent study suggested that 8OHdG was not the proper biomarker [32]. The limitations in animal models of NDs, especially for PD, can be a possible reason for the difference of therapy effects [33]. Finally, there was minimal evidence for therapeutic strategies to target atypical parkinsonian disorders due to difficulty with early diagnosis.

The potential limitations should also be considered. Although we strictly performed the search as described in the methods, and identified 16 studies, we cannot assert there are no other unpublished studies that we failed to identify. Concerning the uncertain data expressed by graphs, no additional information was available in contacting the related authors. It definitely affected the completeness of evidence. A total of six RCTs were included in the meta-analysis; therefore, publication bias could not be examined by funnel plots.

5 Conclusions

There are insufficient data to support the usage of creatine, CoQ10 or its analogues in improving motor symptoms in patients with PD, PSP or HD. High-dose idebenone seems to be promising for FA patients, as measured by ICARS score. Regarding other symptoms, the findings are controversial but certain benefits are detected in creatine, CoQ10 or idebenone compared with placebo. Meanwhile, all these positive results need to be further confirmed by future well-designed studies.

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Conflict of interest Jia Liu and Lu-ning Wang declare no conflicts of interest.

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