Negative results

The effect of long-term treatment with coenzyme Q10 on nucleic acid modifications by oxidation in children with Down syndrome

Emil List Larsen a, b, Lucia Padella c, Helle Kirstine Mørup Bergholdt a, b, Trine Henriksen a, b, Lucia Santoro c, Orazio Gabrielli c, Henrik Enghusen Poulsen a, b, d, e, Gian Paolo Littarru e, Patrick Orlando f, Luca Tiano f

a Laboratory of Clinical Pharmacology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark
b Department of Clinical Pharmacology, Bispebjerg Frederiksberg Hospital, University of Copenhagen, Copenhagen, Denmark
c Pediatric Clinic Laboratory, Department of Clinical Sciences, Children Hospital Salesi, Polytechnic University of Marche, Ancona, Italy
d Department of Clinical Sciences, Polytechnic University of Marche, Ancona, Italy
e Department of Life and Environmental Sciences, Polytechnic University of Marche, Ancona, Italy
f Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

Article info

Article history:
Received 16 November 2017
Received in revised form 25 February 2018
Accepted 1 March 2018
Available online 15 March 2018

Keywords:
Down syndrome
Oxidative stress
Oxidative nucleic acid modifications
8-Oxo-7,8-dihydro-2'-deoxyguanosine
8-Oxo-7,8-dihydroguanosine

Abstract

Elevated levels of oxidative nucleic acid modifications have been proposed to be associated with some of the clinical characteristics of Down syndrome. Oral intake of coenzyme Q10 improves oxidative status and shows a tendency toward protective effect on DNA oxidation in certain age groups of children with Down syndrome. Here, we demonstrate that long-term (i.e., 4 years) treatment with coenzyme Q10 (ubiquinone) at the dosage of 4 mg/kg/d does not affect whole body DNA and RNA oxidation.

1. Introduction

Down syndrome is the result of complete or partial trisomy of chromosome 21 and characterized by elevated levels of oxidative nucleic acid modifications compared to disease free controls (Nunomura et al., 2000; Pallardó et al., 2006). The elevated levels of oxidative modifications are hypothesized to accelerate neuronal degeneration (Capone, 2001) and induce some of the clinical characteristics of the disease, for example, early development of Alzheimer's disease (Zana et al., 2007).

Coenzyme Q10 (CoQ10) is essential in the mitochondrial respiratory chain and has an antioxidative effect on plasma lipids (Littarru and Tiano, 2010). Oral supplementation with ubiquinol at the dosage of 10 mg/kg/d improves plasma oxidative status by increasing the ubiquinol-10:total CoQ10-ratio in children with Down syndrome (Miles et al., 2007). Ubiquinol is the reduced and active form of CoQ10 that became available while this trial was ongoing. This study is the final act of a triple set of experimental studies investigating the protective effect of CoQ10 in the oxidized form (i.e., ubiquinone) at the dosage of 4 mg/kg/d on nucleic acid modifications by oxidation in children with Down syndrome. The first study demonstrated no effect of short-term treatment (i.e., 6 months) with CoQ10 on DNA oxidation (Tiano et al., 2011), in contrast, the second study demonstrated promising results in certain age groups of prolonged treatment (i.e., 20 months) (Tiano et al., 2012). Thus, the primary objective of this study was to evaluate the effect of long-term (i.e., 4 years) treatment with CoQ10 on whole body DNA and RNA oxidation, measured as urinary excretion of 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxodG) and 8-oxo-7,8-dihydroguanosine (8-oxoGuo), in children with Down syndrome.

2. Materials and methods

Children with Down syndrome (n = 32) were treated with 4 mg/kg/d CoQ10, in the form of ubiquinone, for 4 years. A control group
of children with Down syndrome (n = 14) receiving no treatment was included. Urinary excretion of 8-oxodG and 8-oxoGuo was determined at baseline, and after 2 and 4 years intervention by ultra-performance liquid chromatography tandem mass spectrometry, described elsewhere (Rasmussen et al., 2016). The markers were corrected to urinary flow using specific gravity (SG). Further, we determined DNA oxidation by formamidopyrimidine glycosylase (FPG) comet assay in peripheral blood mononuclear cells to compare 2 methods for determining nucleic acid modification by oxidation. Additional information regarding trial design, participants, intervention, laboratory analyses, and statistics is available as supplementary information.

3. Results

Baseline characteristics of age, weight, cholesterol, DNA oxidation, and RNA oxidation were similar in the 2 groups. The effect of treatment with CoQ10 on urinary excretion of 8-oxodG and 8-oxoGuo is presented in Fig. 1 and analyzed using generalized linear mixed model by maximum likelihood. The model showed that the level of DNA oxidation measured by 8-oxodG/SG changed by −0.16 nM (95% confidence interval [CI]: −2.64; 2.31 nM, p = 0.90) per 2 years, whereas treatment with CoQ10 increased the slope with 1.65 nM (95% CI: −1.31; 4.60 nM, p = 0.28). The level of RNA oxidation measured by 8-oxoGuo/SG changed by −0.95 nM (95% CI: −5.92; 4.01 nM, p = 0.71) per 2 years, whereas treatment with CoQ10 increased the slope with 2.41 nM (95% CI: −3.53; 8.35 nM, p = 0.43).

The results from the FPG comet assay are presented as supplementary information and demonstrated no effect of the treatment with CoQ10 on DNA oxidation measured as median tail intensity. There was no significant correlation between urinary excretion of 8-oxodG and median tail intensity (r = 0.02, p = 0.89), Fig. 2. Detailed results are available as supplementary information.

4. Discussion

This study demonstrates that long-term treatment with CoQ10 (ubiquinone) at the dosage of 4 mg/kg/d does not affect DNA and RNA oxidation in children with Down syndrome.

The lack of correlation between urinary excretion of 8-oxodG and median tail intensity in FPG comet assay could be explained by the theory that not all adducts from the oxidized DNA within the cells are repaired and excreted in the urine. Furthermore, urinary excretion of 8-oxodG is the result of an accumulation over time of DNA oxidation, whereas the comet assay quantifies the cellular steady state of DNA oxidation.

Despite previously promising results in certain age group of treatment with CoQ10 on DNA oxidation in children with Down syndrome (Tiano et al., 2012), we are not able to confirm a protective effect CoQ10 on DNA oxidation or RNA oxidation. However, it is possible that the dosage and form of the active component, CoQ10, is not the optimal for modifying nucleic acid modifications by oxidation. Thus, additional long-term studies are required to
evaluate the efficacy of higher dosage of ubiquinol with respect to these endpoints, and a combination of mitochondrial nutrients is more likely to have better chance of producing a protective effect (Pagano et al., 2014a,b).

Data access and responsibility

The principal investigator, Luca Tiano, had full access to all of the data and takes responsibility for the integrity and accuracy of the data and the decision to publish.

Disclosure statement

All authors declare no conflicts of interest. All authors have completed the Unified Competing Interest form at www.icmje.org/coiDisclosure.pdf (available on request from the corresponding author).

Acknowledgements

We thank Pharma Nord, Denmark, for kindly donating Myoquinon used for the study. We thank Dr. Anna Tangorra for assisting with the comet assay analysis. Further, we thank senior laboratory technician Lis K. Hansen and laboratory technicians Katja L. Christensen for performing the urine analyses. Furthermore, we thank Dr. A. Collins for kindly donating purified FPG. We would also like to thank the participants and their families for making this study possible.

Funding: This study was supported by Marche Polytechnic University Atheneum funding to Gian Paolo Littaru and Luca Tiano.

None of the funding sources were involved in the design, conduct of study, collection, management, analysis, or interpretation of data, preparation or review of article and had no right to approve or disapprove of the submitted article.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.neurobiolaging.2018.03.001.

References