Systematic evaluation of muscle coenzyme Q10 content in children with mitochondrial respiratory chain enzyme deficiencies

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Abstract
Coenzyme Q10 content, pathology evaluation, and electron transport chain (ETC) enzyme analysis were determined in muscle biopsy specimens of 82 children with suspected mitochondrial myopathy. Data were stratified into three groups: “probable” ETC defects, “possible” ETC defects, and disease controls. Muscle total, oxidized, and reduced coenzyme Q10 concentrations were significantly decreased in the probable defect group. Stepwise logistic regression indicated that only total coenzyme Q10 was significantly associated with probable ETC defect. Receiver operator characteristic (ROC) analysis suggested that total muscle coenzyme Q10 was the best predictor of an ETC complex abnormality. Determination of muscle coenzyme Q10 deficiency in children with suspected mitochondrial disease may facilitate diagnosis and encourage earlier supplementation of this agent.

1. Introduction
Mitochondria are cellular organelles which are ubiquitous in eukaryotes, and essential for the support of aerobic respiration and production of adenosine triphosphate (ATP). Defects in mitochondrial function may result from mutations in nuclear- or mitochondrial-encoded genes. Adult patients who present as a “classical” mitochondrial syndrome are usually screened for common mitochondrial DNA (mtDNA) mutations as a first step in diagnosis process. However, the diagnosis of mitochondrial disease in infants and children is generally more complex and difficult than in adults, in part because of non-specific clinical features and infrequent genetic abnormalities (Carrozzo et al., 2007).

Although once thought to be rare, the influx of new reports of coenzyme Q10 deficiency suggests that this disorder may be much more common than previously thought (Ogasahara et al., 1989; Sobreira et al., 1997; Boitier et al., 1998; Di Giovanni et al., 2001; Musumeci et al., 2001; Rahman et al., 2001; Van Maldergem et al., 2002; Lamperti et al., 2003; Aure et al., 2004; Gironi et al., 2004; Lalani et al., 2005; Salviati et al., 2005; López et al., 2006; Horvath et al., 2006; Artuch et al., 2006; Gempel et al., 2007; Le Ber et al., 2007). Primary coenzyme Q10 deficiency (MIM 607426) is an autosomal recessive condition with a broad clinical spectrum (DiMauro, 2006), and at least five phenotypes of human coenzyme Q10 deficiency have been characterized (Munnich and Rustin, 2001; DiMauro et al., 2007a,b; Quinzii et al., 2007a).
Thus, far primary coenzyme muscle Q10 deficiency has been associated with three of the nine genes thought to be involved in the biosynthesis of coenzyme Q10 (DiMauro et al., 2007a). Quinzii et al. reported a mutation in the COQ2 gene of two patients with encephalomyopathy and nephropathy (Quinzii et al., 2006). A second cause of primary coenzyme Q10 deficiency was described by Lopez et al., who reported a male infant with severe Leigh syndrome, nephrotic syndrome, coenzyme Q10 deficiency in muscle and fibroblasts, and compound heterozygous mutations in the decaprenyl diphosphate synthase subunit 2 (PDSS2) gene (Lopez et al., 2006). The PDSS2 gene encodes the second subunit of decaprenyl diphosphate synthase synthase, which is considered as one of the rate-limiting enzymes in coenzyme Q10 biosynthesis. Mollet et al. described mutations in two genes, i.e. COQ2 and PDSS1, associated with the coenzyme Q10 biosynthesis pathway in members of two unrelated families (Mollet et al., 2007). Marked depletion of muscle coenzyme Q10 was reported in these cases of primary deficiency.

Secondary coenzyme Q10 deficiency in mitochondrial myopathy has been suggested by mutations in two nuclear encoded genes. A homozygous mutation in the aprataxin (APTX) gene was associated with low muscle coenzyme Q10 levels in five patients, including three affected siblings, with ataxia and oculomotor apraxia 1 (Le Ber et al., 2007). Autosomal recessive mutations in the electron-transferring-flavoprotein dehydrogenase (ETFDH) gene have been identified in the isolated myopathic form of muscle coenzyme Q10 deficiency in five patients from independent families (Gempel et al., 2007). These patients, whose age of onset ranged from 12 to 32 years, had milder depletion of muscle coenzyme Q10 (Gempel et al., 2007).

Differences in primary and secondary forms of coenzyme Q10 deficiency have diagnostic relevance. Primary coenzyme Q10 deficiency is more commonly associated with younger onset, severe disease, and profound depletion of muscle coenzyme Q10, while secondary deficiency tends to be less severe, later in onset, and results in milder depletion of coenzyme Q10 in affected tissues. One aspect, which may be shared by both primary and secondary types of this deficiency, is the general agreement that early diagnosis may increase the benefits afforded by coenzyme Q10 supplementation to these patients (Musumeci et al., 2001; Di Giovanni et al., 2001; Gironi et al., 2004; Scaglia et al., 2004; Lalani et al., 2005; Saviti et al., 2005; Artuch et al., 2006; Finsterer, 2006; Dimarco and Mancuso, 2007b). For the interested reader a more complete discussion of the genetics of coenzyme Q10 deficiency was published by Quinzii et al. (2007b).

The current study will evaluate muscle coenzyme Q10 content and electron transport chain (ETC) complex dysfunction in a general population of children with suspected, but unproven, mitochondrial myopathic disease. Specifically, the study objectives are to characterize the relationship between muscle total, reduced, and oxidized coenzyme Q10 content and ETC complex deficiency, and to determine whether muscle coenzyme Q10 testing may be a useful test for evaluation of ETC abnormalities in children with suspected mitochondrial disorders.

2. Patients and methods

This study was approved by the Cincinnati Children’s Hospital Medical Center (CCHMC) Institutional Review Board, Cincinnati, OH. Muscle specimens were collected from biopsies of 82 children (mean age 5.4 years; range 0.2–16.6 years) between January, 2004 and March, 2006. Open biopsy of muscle was ordered by the attending physician because of suspected mitochondrial myopathy. Seventy-five of 82 (92%) specimens were from the Quadriceps femoris. Fresh specimens were immediately delivered to the CCHMC Division of Pathology and Laboratory Medicine. Each specimen was examined by two experienced muscle pathologists for microscopic, histological, and ultrastructural evidence of mitochondrial disease. The percentage of myofibers with subsarcolemmal mitochondria aggregates (SSMA) was counted in a representative high-power field of 100–300 myofibers using succinate dehydrogenase (SDH) stained slides (Miles et al., 2005). A subgroup of SSMA, i.e. large SSMA, was also determined. The large SSMA group was defined as the thickness of SSMA > 3 μm and/or multifocal mitochondrial aggregates (≥3) in the same myofiber cross-section (Miles et al., 2006). The numerical proportion of type 1 myofibers was estimated, and specimens with 60% or more of type 1 myofibers were classified as type 1 myofiber predominant. Ultrastructural evidence for possible mitochondriopathy was defined by the presence of unequivocally pathologic mitochondria based upon size, abnormal arrangement of cristae, abnormal mitochondrial matrix density or matrix inclusions, and/or increased intermyofibrillar lipid.

A portion of each muscle specimen was frozen and shipped to the Center for Inherited Disorders of Energy Metabolism at Rainbow Babies and Children’s Hospital, Cleveland, OH, for ETC complex analysis. Excess residual muscle (approximately 20–40 mg) was flash frozen within 10 min after collection, and stored at −70 °C until coenzyme Q10 analysis. Oxidized, reduced, and total coenzyme Q10 content were measured in each muscle specimen by HPLC with electrochemical detection in the CCHMC Clinical Laboratory (Tang et al., 2004). Total protein content of each specimen was determined as an index for coenzyme Q10 content as described previously (Tang et al., 2004). Clinical laboratory personnel were blinded from personal identifiers associated with muscle specimens.

Patients’ data were stratified by the presence or absence of ETC complex defects based upon the percentage of each ETC complex activity compared with the respective mean control activity. Patients with one or more ETC complexes ≤30% of the respective mean control value were defined, for the purposes of this study, as “probable” for ETC defect. Although this cutoff is somewhat arbitrary, it is analogous to criteria for abnormal mitochondrial
respiratory chain enzyme function suggested by others (Walker et al., 1996; Bernier et al., 2002; Thorburn et al., 2004; Scaglia et al., 2004; Montero et al., 2005). It should also be noted that most do not consider an ETC complex defect in muscle as “definitive” for mitochondrial disease unless it is <20% of the mean control activity (Walker et al., 1996; Bernier et al., 2002; Thorburn et al., 2004; Scaglia et al., 2004; Montero et al., 2005). In order to provide further evidence of the linearity of the muscle coenzyme Q10 content determination in a mixed population, a less stringent cutoff range, i.e. from >30% to ≤40% of the mean control ETC complex activity, was defined as “possible” for ETC complex defect.

A control group with normal ETC activity and without evidence of muscle disease was selected from the 82 muscle specimens based upon the following criteria: all patients with (1) >65% activity for citrate synthase (expressed as the percent of the laboratory mean control value); and (2) activities of all ETC complexes >50% (expressed as the percent of the laboratory mean control value); and (3) no pathologically or clinically diagnosed muscle disease. In addition, these cutoff values for normal ETC activities were well within the laboratory control ranges for each ETC complex and citrate synthase. Because of the potential effect on muscle, patients receiving coenzyme Q10 supplementation recently or at the time of muscle biopsy were excluded from the stratification of study subjects.

In our systematic evaluation bivariate correlations were determined in the initial evaluation of the potential relationships between muscle coenzyme Q10 and pathology measures with ETC complex activities. Spearman coefficients were determined between coenzyme Q10 measurements, SSMA (%), type 1 myofiber predominance (%), and individual ETC complex activities for all participants. Stepwise logistic regression analysis was then performed on the dichotomous dependent variable of probable ETC defect vs. all other participants with ETC test results. The dependent variables included age, type 1 myofiber predominance (%), SSMA (%), total coenzyme Q10, reduced coenzyme Q10, oxidized coenzyme Q10, and coenzyme Q10 redox (reduced:oxidized) ratio.

Receiver operating characteristic (ROC) analysis is widely accepted as the preferred method for characterizing and comparing the overall diagnostic accuracy and validity of laboratory tests or diagnostic measures because it incorporates the trade-off between sensitivity and specificity over the range of that test (Zou et al., 2007). In addition, by maximizing the sum of the sensitivity and the specificity of a test ROC analysis provides the optimal threshold or cutpoint for a test or model (Zou et al., 2007). In our systematic evaluation the ROC analysis parameters for coenzyme Q10 and pathology tests were calculated based upon the likely presence or absence of an ETC defect, as defined by probably ETC complex deficiency. In order to minimize selection bias data from all muscle specimens were dichotomized as either positive (i.e. the 12 in the probable defect group) or negative (all 70 others) for a mitochondrial ETC complex defect.

The statistical method for determination of total coenzyme Q10 reference interval was based on the robust method (Horn et al., 1998). The robust method, which allows reference interval estimation using sample sizes <120, is based on the resistant estimators of location and spread, and generally agrees reasonably well with the traditional Normal-theory intervals (Horn and Pesce, 2005).

3. Results

A total of 82 muscle biopsy specimens were evaluated for ETC complex defects during the study period. After stratification 12 patients met the criteria for probable ETC defect, 11 met criteria for possible ETC defect, and 20 met the criteria for controls. Further evidence of the adequacy of control muscle specimens is provided by ETC complex II activity, which was ≥90% of the laboratory mean control value in all group members.

In order to assess the characteristics of a general population of children with suspected mitochondrial disease, data for all 82 participants were included in bivariate correlations, stepwise logistic regression, and ROC evaluations. Patient characteristics, pathology findings, and ETC complex activities for each study group are summarized in Table 1. The three study groups were similar for age, gender, most clinical findings, and citrate synthase (%) activity (Table 1). Ethnicity differences in the three study groups were observed (Table 1), however these differences were not controllable due to the study design and limited sample size. The frequency of patients with reports of elevated blood lactate >3.33 mmol/L was similar in the three study groups (Table 1).

None of the 82 participants had evidence of ragged-red fibers (RRF), ragged-blue fibers (RBF), or cytochrome c oxidase (COX)-negative myofibers. A slightly increased incidence of type I myofiber predominance (%) in the possible ETC defect group is unlikely an important difference (Table 1). Somewhat surprisingly SSMA (%) was decreased in the probable ETC defect group compared with controls (Table 1). Microscopic abnormalities were non-specific except for one patient with congenital muscular dystrophy in the probable ETC defect group and one with spinal muscular atrophy (SMA) in the possible ETC defect group (Table 1). The muscle total coenzyme Q10 levels measured in these two patients were very low as well, i.e. 99.2 nmol/g protein and 130.7 nmol/g protein, respectively. It is interesting to note that muscle ETC abnormalities have been reported previously in both of these neuromuscular diseases (Berger et al., 2003; Jongpiputvanich et al., 2005). Agreement between low ETC complex activities and total coenzyme Q10 levels in these two patients helps to clarify and validate the study objectives. No pathologic mitochondrial abnormalities were observed by EM in any patient in the three study groups (Table 1).
As expected, significantly lower ETC complex enzyme activities were evident in the probable and possible defect groups compared with the control group (Table 1). Several patients had genetic studies conducted for gene mutations associated with mitochondrial myopathies. Only one patient in the possible ETC defect group was determined to have a genetic mutation associated with mitochondrial defect or syndrome, i.e. Leigh syndrome.

Muscle coenzyme Q10 results are summarized in Table 2. Mean total and oxidized coenzyme Q10 levels were decreased in the probable ETC defect group compared with the control group (Table 2). All patients in the probable ETC defect group had complex I + III and/or II + III defects, except for one who had a complex III defect. Analysis of data from all 82 participants showed significant bivariate correlations between total coenzyme Q10, reduced coenzyme Q10, oxidized coenzyme Q10, and SSMA (%) vs. individual ETC enzyme activities (Table 3). Significant correlations were not observed between coenzyme Q10 redox (reduced:oxidized) ratio and type 1

![Image](https://via.placeholder.com/150)

Table 1: Summary of patient clinical features, laboratory and pathology findings

<table>
<thead>
<tr>
<th></th>
<th>Controls (n = 20)</th>
<th>Possible ETC defect (n = 11)</th>
<th>Probable ETC defect (n = 12)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>7.0 (5.2)</td>
<td>4.4 (3.5)</td>
<td>3.3 (3.2)</td>
<td>0.180, a 0.062 ,b 0.389,c</td>
</tr>
<tr>
<td>Sex (F) (%)</td>
<td>7 (35)</td>
<td>5 (45)</td>
<td>5 (42)</td>
<td>0.705, a 0.724,b 1.000,c</td>
</tr>
<tr>
<td>Ethnicity (W/AA/other)</td>
<td>19/1/0</td>
<td>9/1/1</td>
<td>7/2/3</td>
<td>0.436, a 0.018,b 0.562,c</td>
</tr>
<tr>
<td>Muscle weakness or hypotonia (%)</td>
<td>13 (65)</td>
<td>4 (36)</td>
<td>4 (33)</td>
<td>0.154, a 0.144,b 1.000,c</td>
</tr>
<tr>
<td>Developmental/motor delay (%)</td>
<td>8 (40)</td>
<td>5 (45)</td>
<td>3 (25)</td>
<td>1.000, a 0.465,b 0.409,c</td>
</tr>
<tr>
<td>Epilepsy (%)</td>
<td>10 (50)</td>
<td>4 (36)</td>
<td>0 (0)</td>
<td>0.707, a 0.004,b 0.037,c</td>
</tr>
<tr>
<td>Blood lactate &gt;3.33 mmol/L (% tested)</td>
<td>2/16 (13)</td>
<td>2/9 (22)</td>
<td>2/9 (22)</td>
<td>0.602, a 0.602,b 1.000,c</td>
</tr>
<tr>
<td>Light microscopy abnormality (%)</td>
<td>0 (0)</td>
<td>5 (45)d</td>
<td>7 (58)e</td>
<td>0.003, a 0.0002,b 0.684,c</td>
</tr>
<tr>
<td>Electron microscopy abnormality (%)</td>
<td>0/20 (0)</td>
<td>0/10 (0)</td>
<td>0/11 (0)</td>
<td>--</td>
</tr>
<tr>
<td>Subsarcolemmal mitochondrial aggregates (%)</td>
<td>7.0 (5.9)</td>
<td>5.5 (6.2)</td>
<td>4.6 (6.0)</td>
<td>0.331, a 0.050,b 0.663,c</td>
</tr>
<tr>
<td>Type I myofiber predominance (%)</td>
<td>41.1 (8.2)</td>
<td>50.3 (10.7)</td>
<td>48.5 (17.6)</td>
<td>0.202, a 0.255,b 0.749,c</td>
</tr>
<tr>
<td>Citrate synthase (%)</td>
<td>98.0 (23.3)</td>
<td>85.1 (34.6)</td>
<td>84.4 (32.1)</td>
<td>0.107, a 0.414,b 0.498,c</td>
</tr>
<tr>
<td>Complex I (%)</td>
<td>112.3 (35.9)</td>
<td>103.3 (71.9)</td>
<td>68.9 (19.9)</td>
<td>0.035, a 0.0002,b 0.049,c</td>
</tr>
<tr>
<td>Complex I + III (%)</td>
<td>109.4 (52.3)</td>
<td>45.9 (17.4)</td>
<td>34.6 (27.1)</td>
<td>0.001, a 0.0001,b 0.005,c</td>
</tr>
<tr>
<td>Complex I + III (%)</td>
<td>179.9 (81.5)</td>
<td>73.2 (43.2)</td>
<td>0.027, a 0.027,c</td>
<td></td>
</tr>
<tr>
<td>Complex I + III (%)</td>
<td>102.0 (63.4)</td>
<td>53.4 (29.9)</td>
<td>33.2 (19.6)</td>
<td>0.001, a 0.0001,b 0.042,c</td>
</tr>
<tr>
<td>Complex III (%)</td>
<td>109.9 (39.9)</td>
<td>113.1 (63.8)</td>
<td>61.4 (53.5)</td>
<td>0.665, a 0.001,b 0.019,c</td>
</tr>
<tr>
<td>Complex IV (%)</td>
<td>109.9 (49.2)</td>
<td>60.4 (13.6)</td>
<td>66.2 (31.6)</td>
<td>0.0001, a 0.004,b 0.951,c</td>
</tr>
</tbody>
</table>

Mean (SD) except where indicated otherwise.

- a Possible ETC defect group vs. control group; (Fisher’s Exact Test or Mann–Whitney U Test).
- b Probable ETC defect group vs. control group; (Fisher’s Exact Test or Mann–Whitney U Test).
- c Probable ETC defect group vs. possible ETC defect group; (Fisher’s Exact Test or Mann–Whitney U Test).
- d Including two with type I myofiber predominance; two with type I and/or type II myofiber atrophy; and one with spinal muscle atrophy.
- e Including four with type I myofiber predominance; two with type I and/or type II myofiber atrophy; and one with congenital muscular dystrophy.
- f Expressed as percent of the laboratory control mean value.
- g NADH-ferricyanide reductase.
- h NADH-cytochrome c reductase (rotenone sensitive).
- i Succinate dehydrogenase.
- j Succinate-cytochrome c reductase (antimycin sensitive).
- k Decylubiquinol-cytochrome c reductase.
- l Cytochrome c oxidase.

As expected, significantly lower ETC complex enzyme activities were evident in the probable and possible defect groups compared with the control group (Table 1). Several patients had genetic studies conducted for gene mutations associated with mitochondrial myopathies. Only one patient in the possible ETC defect group was determined to have a genetic mutation associated with mitochondrial defect or syndrome, i.e. Leigh syndrome.

Muscle coenzyme Q10 results are summarized in Table 2. Mean total and oxidized coenzyme Q10 levels were decreased in the probable ETC defect group compared with the control group (Table 2). All patients in the probable ETC defect group had complex I + III and/or II + III defects, except for one who had a complex III defect. Analysis of data from all 82 participants showed significant bivariate correlations between total coenzyme Q10, reduced coenzyme Q10, oxidized coenzyme Q10, and SSMA (%) vs. individual ETC enzyme activities (Table 3). Significant correlations were not observed between coenzyme Q10 redox (reduced:oxidized) ratio and type I

Table 2: Comparison of coenzyme Q10 (CoQ10) test results

<table>
<thead>
<tr>
<th></th>
<th>Controls (n = 20)</th>
<th>Possible ETC defect (n = 11)</th>
<th>Probable ETC defect (n = 12)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total CoQ10 (nmol/g protein)</td>
<td>214.9 (48.8)</td>
<td>205.8 (67.0)</td>
<td>165.2 (70.8)</td>
<td>0.901, a 0.027,b 0.124,c</td>
</tr>
<tr>
<td>Reduced CoQ10 (nmol/g protein)</td>
<td>77.3 (22.9)</td>
<td>70.1 (41.0)</td>
<td>59.9 (32.6)</td>
<td>0.364, a 0.052,b 0.460,c</td>
</tr>
<tr>
<td>Oxidized CoQ10 (nmol/g protein)</td>
<td>137.6 (37.3)</td>
<td>135.7 (45.3)</td>
<td>105.4 (43.8)</td>
<td>0.934, a 0.047,b 0.074,c</td>
</tr>
<tr>
<td>Reduced:oxidized CoQ10 ratio</td>
<td>0.59 (0.23)</td>
<td>0.54 (0.30)</td>
<td>0.57 (0.17)</td>
<td>0.563, a 0.669,b 0.538,c</td>
</tr>
</tbody>
</table>

Mean (SD).

- a Possible ETC defect group vs. control group; (Mann–Whitney U Test).
- b Probable ETC defect group vs. control group; (Mann–Whitney U Test).
- c Probable ETC defect group vs. possible ETC defect group; (Mann–Whitney U Test).
myofiber predominance (%) vs. individual ETC complex activities (Table 3).

Stepwise logistic regression found that total coenzyme Q10 content was the only factor significantly associated with a probable ETC complex defect \((P = 0.009\) based on Wald \(\chi^2\)). This model indicates that for every 10 nmol/g protein decrease in muscle total coenzyme Q10, there would be 14.9% increase in the odds of a patient having an ETC complex defect (95% Wald CI for increase in odds ratio: 3.5%, 27.6%).

Comparison of areas under the ROC curves for total, oxidized, and reduced coenzyme Q10, and pathology measures for an ETC complex defect indicated that total coenzyme Q10 content was the best predictor (Table 4). It should be understood that data from all 82 participants were included in this assessment to lessen the potential for selection bias. Based upon the cutoff value determined by the ROC analysis, patients having muscle total coenzyme Q10 content <185 nmol/g protein would have a significantly greater risk of an ETC complex defect than patients with > 185 nmol/g protein. This cutoff value may increase the usefulness of muscle coenzyme Q10 testing, because it provides a means of screening for a potential ETC complex defects.

The robust reference interval for total coenzyme Q10, i.e. 107–317 nmol/g protein, was derived for the disease control group. The lower limit of the resulting 95% reference interval may be useful for predicting or confirming

| Table 3 |

<p>| Bivariate correlation of skeletal muscle coenzyme Q10 (CoQ10) and pathology measures ((n = 82)) with mitochondrial electron transport chain complex activities (expressed as percent of laboratory mean control value) |</p>
<table>
<thead>
<tr>
<th>Complex I^a</th>
<th>Complex I + III^b</th>
<th>Complex II^c</th>
<th>Complex II + III^d</th>
<th>Complex III^e</th>
<th>Complex IV^f</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total CoQ10 (nmol/g protein)</td>
<td>0.2701(^{i})</td>
<td>0.2406</td>
<td>0.4279</td>
<td>0.3245</td>
<td>0.1922</td>
</tr>
<tr>
<td>Reduced CoQ10 (nmol/g protein)</td>
<td>0.0141(^{i})</td>
<td>0.0295</td>
<td>(&lt;0.0001)</td>
<td>0.0029</td>
<td>0.0836</td>
</tr>
<tr>
<td>Oxidized CoQ10 (nmol/g protein)</td>
<td>0.2407</td>
<td>0.2586</td>
<td>0.2976</td>
<td>0.2454</td>
<td>0.1904</td>
</tr>
<tr>
<td>CoQ10 redox ratio^g</td>
<td>0.294</td>
<td>0.0190</td>
<td>0.0666</td>
<td>0.0263</td>
<td>0.0866</td>
</tr>
<tr>
<td>Myofiber (%) with SSMA^h</td>
<td>0.2522</td>
<td>0.2425</td>
<td>0.4009</td>
<td>0.3341</td>
<td>0.1936</td>
</tr>
<tr>
<td>Type 1 Myofiber predominance (%)</td>
<td>0.0222</td>
<td>0.0281</td>
<td>0.0002</td>
<td>0.0022</td>
<td>0.0814</td>
</tr>
</tbody>
</table>

\(^{a}\) NADH-ferricyanide reductase.
\(^{b}\) NADH-cytochrome c reductase (rotenone sensitive).
\(^{c}\) Succinate dehydrogenase.
\(^{d}\) Succinate-cytochrome c reductase (antimycin sensitive).
\(^{e}\) Decylubiquinol-cytochrome c reductase.
\(^{f}\) Cytochrome c oxidase.
\(^{g}\) CoQ10 redox ratio, ratio of reduced CoQ10 to oxidized CoQ10.
\(^{h}\) SSMA, mean percentage of myofibers with subsarcolemmal mitochondrial aggregates per microscopic field.

Data format:
\(^{i}\) Spearman correlation coefficient.
\(^{j}\) Prob. > \(|r|\) under H0: Rho = 0.

| Table 4 |

<p>| Comparison of the discriminative performance of muscle coenzyme Q10 (CoQ10) and pathology testing results for probable electron transport chain (ETC) defects ((n = 12)) vs. all other participants with ETC testing ((n = 70)) |</p>
<table>
<thead>
<tr>
<th>Test</th>
<th>AUC(^a)</th>
<th>Cutoff value(^b)</th>
<th>(P)-value(^c)</th>
<th>Sensitivity</th>
<th>95% CI</th>
<th>Specificity</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total CoQ10 (nmol/g protein)</td>
<td>0.77</td>
<td>(&lt;185.1)</td>
<td>(&lt;0.001)</td>
<td>75.0</td>
<td>51.6, 94.5</td>
<td>81.4</td>
<td>72.0, 89.7</td>
</tr>
<tr>
<td>Oxidized CoQ10 (nmol/g protein)</td>
<td>0.76</td>
<td>(&lt;110.9)</td>
<td>(&lt;0.001)</td>
<td>66.7</td>
<td>42.9, 90.0</td>
<td>81.4</td>
<td>72.0, 89.7</td>
</tr>
<tr>
<td>SSMA^d (%)</td>
<td>0.72</td>
<td>(&lt;7.0)</td>
<td>0.011</td>
<td>91.7</td>
<td>73.6, 99.7</td>
<td>52.9</td>
<td>42.0, 64.9</td>
</tr>
<tr>
<td>Reduced CoQ10 (nmol/g protein)</td>
<td>0.70</td>
<td>(&lt;63.3)</td>
<td>0.028</td>
<td>75.0</td>
<td>51.6, 94.5</td>
<td>72.9</td>
<td>62.5, 82.8</td>
</tr>
<tr>
<td>Type 1 Myofiber (%) predominance</td>
<td>0.51</td>
<td>(&lt;30.0)</td>
<td>0.86</td>
<td>18.2</td>
<td>6.1, 51.7</td>
<td>94.2</td>
<td>87.9, 98.3</td>
</tr>
<tr>
<td>CoQ10 redox ratio(^e)</td>
<td>0.50</td>
<td>(&lt;0.90)</td>
<td>1.00</td>
<td>100.0</td>
<td>n/a</td>
<td>10.0</td>
<td>5.1, 19.5</td>
</tr>
</tbody>
</table>

\(^{a}\) AUC, area under the receiver operating characteristic (ROC) curve.
\(^{b}\) Cutoff value, point of maximum test sensitivity and specificity.
\(^{c}\) \(P\)-value, receiver operating characteristic (ROC) AUC compared with AUC = 0.50.
\(^{d}\) Mean percentage of myofibers with subsarcolemmal mitochondrial aggregates per microscopic field.
\(^{e}\) Ratio of reduced CoQ10 to oxidized CoQ10.
primary and secondary muscle coenzyme Q10 deficiencies, but further studies are needed to validate this reference interval.

4. Discussion

4.1. Study objectives and novel findings

The first study objective was to characterize the relationship between muscle total, reduced, and oxidized coenzyme Q10 content and ETC complex deficiency. As far as we can determine the current study is the first to systematically relate muscle coenzyme Q10 content with various levels of ETC complex dysfunction in children with suspected mitochondrial disorders. Again, as far as we can determine this is the first study to use ROC analysis, which is the preferred method for evaluating diagnostic test accuracy and validity, to demonstrate that total coenzyme Q10 is the most reliable testing measure in the current study related to ETC complex dysfunction (Table 4). Establishing a scientifically based cutoff and a reference interval for the interpretation of muscle coenzyme Q10 levels should improve the usefulness of this test.

Some investigators have advocated coenzyme Q10 redox status as a potential biomarker for oxidative stress (Yamamoto and Yamashita, 1999; Hara et al., 1999; Galinier et al., 2004), however the results of the current study do not support this claim. The current results indicate that coenzyme Q10 redox (reduced:oxidized) ratio is unchanged in the three study groups (Table 2), and is not correlated with any ETC complex activity (Table 3). Therefore, measurement of the reduced and oxidized forms of coenzyme Q10 in muscle appears to be unnecessary for assessment of coenzyme Q10 deficiency.

4.2. Study limitations

It should be noted that the disproportionate ethnic representation in study groups (Table 1) was not a factor which could be controlled due to the study design, but ethnic differences should be considered in future studies. The current study has attempted to define a control group, which is similar in age to the study groups, has normal ETC complex activities, and no pathological evidence of muscle disease. Control groups in previous reports were frequently inadequately defined (Table 5), which limits their ability to ascribe “abnormality” to their findings. Although no individuals in the current disease control group had diagnostic abnormality by pathologic exam, we cannot exclude the possibility that some may have had undiagnosed muscle disease. It should also be noted, however, that three patients (25%) in the probable ETC defect group and one (9%) in the possible group had muscle coenzyme Q10 content less than the proposed reference interval. This finding supports the hypothesis that muscle ETC complex deficiency, especially in relation to complexes I + III and II + III, is associated with low coenzyme Q10 content.

Because few patients had been studied for potential genetic causes of mitochondrial disease, the possibility that some may have had genetic mutations associated with mitochondrial disease cannot be ruled out. Thus, the current report is unable to comment upon possible relationships between genetic mutations and muscle coenzyme Q10 content.

Another limitation may be due to the fact that no participant had isolated defects in ETC complexes I, II, or IV. All but one in probable study group had a complex I + III or II + III defect. According to one report ETC defects involving complex I + III or complex II + III are predominant in patients with primary coenzyme Q10 deficiency (Quinzi et al., 2007a). Another report determined that six of 13 patients (ages unspecified), who showed “partial” low complex I + III or complex II + III activity (defined as <40% of the mean control value), also had low muscle coenzyme Q10 <86 nmol/g protein (Montero et al., 2005). The link between coenzyme Q10 deficiency and dysfunction of complexes I + III and II + III is expected, because low coenzyme Q10 availability in mitochondria would impair electron transfer from complexes I and II to complex III and cause defective ATP production (Sobreira et al., 1997). Further studies are needed to clarify the relationship between muscle coenzyme Q10 deficiency and other diseases associated with defects in ATP production.

The importance of interpreting test results in the context of other patient clinical and laboratory findings is a limitation for many types of clinical laboratory testing. One patient in the probable ETC defect group with marked depletion of total coenzyme Q10 concentration (37.1 nmol/g protein) illustrates this point. This patient was considered unlikely to have a primary coenzyme Q10 deficiency because the pathologic examination showed a significant proportion of fibrous tissue associated with the muscle specimen. Because the current analytical method for muscle coenzyme Q10 normalizes for total protein content (Tang et al., 2004), it is possible that this result was affected by increased protein content in the fibrous tissue. On the other hand normalizing to protein content is more robust because it increases the ability to compare coenzyme Q10 content from a variety of tissues and cell types. This example illustrates the importance of careful triage of all muscle specimens from patients with suspected metabolic disorders, especially when an ETC complex defect is suspected.
## Table 5

Summary of participant characteristics and treatment responses in reports of five phenotypes of muscle coenzyme Q10 (CoQ10) deficiency

<table>
<thead>
<tr>
<th>Phenotype group</th>
<th>references</th>
<th>n/Sex</th>
<th>Age (years)</th>
<th>Notable pathology/genetics</th>
<th>Deficient, etc. complex(S)</th>
<th>Control group</th>
<th>(^b)CoQ10 Treatment response</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Encephalomyopathy</strong></td>
<td>Ogasahara et al. (1989)</td>
<td>2/F</td>
<td>12, 14</td>
<td>ELS, SSMA</td>
<td>I + III, II + III</td>
<td>4, 5</td>
<td>Without muscle disease (n = 8)</td>
</tr>
<tr>
<td></td>
<td>Sobrera et al. (1997)</td>
<td>1/F</td>
<td>35</td>
<td>RRF, COX-deficient myofibers, ELS</td>
<td>I + III, II + III</td>
<td>8</td>
<td>Unspecified (n = 9)</td>
</tr>
<tr>
<td></td>
<td>Boitier et al. (1998)</td>
<td>1/M</td>
<td>4</td>
<td>RRF, irregular type I myofibers, SSMA, ELS</td>
<td>I + III, II + III</td>
<td>16</td>
<td>Healthy patients(^c) (n = 20)</td>
</tr>
<tr>
<td></td>
<td>Di Giovanni et al. (2001)</td>
<td>2/M</td>
<td>12, 15</td>
<td>RRF, ELS</td>
<td>I + III, II + III</td>
<td>35, 39</td>
<td>Unspecified</td>
</tr>
<tr>
<td><strong>Multisystemic infantile disease</strong></td>
<td>Rahman et al. (2001)</td>
<td>1/M</td>
<td>0.1</td>
<td>Type 2B myofiber atrophy, ELS</td>
<td>I + III</td>
<td>(~10^d)</td>
<td>Unspecified</td>
</tr>
<tr>
<td></td>
<td>Salviati et al., 2005</td>
<td>1/M</td>
<td>2.7</td>
<td>WNL</td>
<td>I + III, II + III</td>
<td>38</td>
<td>Unspecified (n = 118)</td>
</tr>
<tr>
<td><strong>Cerebellar ataxia</strong></td>
<td>Musumeci et al. (2001)</td>
<td>3/F, 3/M</td>
<td>11–25</td>
<td>Non-specific abnormalities</td>
<td>WNL</td>
<td>26–35</td>
<td>Without muscle disease (n = 30)(^f)</td>
</tr>
<tr>
<td></td>
<td>Lamperi et al. (2003)</td>
<td>8/F, 5/M</td>
<td>0.2–9</td>
<td>WNL</td>
<td>I + III, II + III</td>
<td>13–64</td>
<td>Disease controls(^e) (n = 117)</td>
</tr>
<tr>
<td></td>
<td>Gironi et al. (2004)</td>
<td>2/M</td>
<td>35, 48</td>
<td>Mild neurogenic changes</td>
<td>Not reported</td>
<td>49, 57</td>
<td>Normal muscle(^e) (n = 121)</td>
</tr>
<tr>
<td></td>
<td>Artuch et al. (2006)</td>
<td>1/F</td>
<td>12</td>
<td>SSMA</td>
<td>I + III, II + III</td>
<td>(~17^d)</td>
<td>Unspecified</td>
</tr>
<tr>
<td></td>
<td>Le Ber et al. (2007)</td>
<td>5/M</td>
<td>17–34</td>
<td>Mild neurogenic atrophy/ homozygous for the W279X mutation in the AOA1 gene</td>
<td>WNL</td>
<td>(~55^{d}) (range 42–66)</td>
<td>Defined (n = 22) median age 28 years (range 0.8–67 years)(^h)</td>
</tr>
<tr>
<td><strong>Isolated myopathy</strong></td>
<td>Aure et al. (2004)</td>
<td>1/F</td>
<td>5</td>
<td>SSMA, ELS</td>
<td>I + III, II + III</td>
<td>(&lt;4^d)</td>
<td>Unspecified</td>
</tr>
<tr>
<td></td>
<td>Lalani et al. (2005)</td>
<td>1/M</td>
<td>11.5</td>
<td>RRF</td>
<td>I, I + III</td>
<td>46</td>
<td>Unspecified</td>
</tr>
<tr>
<td></td>
<td>Gempel et al. (2007)</td>
<td>2/F, 3/M</td>
<td>12–32</td>
<td>ELS/autosomal recessive mutations in ETFDH gene</td>
<td>I, II + III, IV</td>
<td>(~17^{d}) (range 13–27)</td>
<td>Defined(n = 25)(^{e,h})</td>
</tr>
<tr>
<td><strong>Leigh syndrome with growth retardation, ataxia, and deafness</strong></td>
<td>Van Maldergem et al. (2002)</td>
<td>1/F</td>
<td>31</td>
<td>RRF, ELS</td>
<td>II + III</td>
<td>5</td>
<td>Unspecified</td>
</tr>
<tr>
<td></td>
<td>López et al. (2006)</td>
<td>1/M</td>
<td>0.3</td>
<td>SSMA/heterozygous mutations in the PDSS2 gene</td>
<td>II + III</td>
<td>14</td>
<td>Unspecified (n = 185)</td>
</tr>
</tbody>
</table>

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*ETC, electron transport chain; ELS, excess lipid storage; RRF, ragged red fibers; SSMA, subsarcolemmal mitochondrial aggregates; WNL, within normal limits; CK, creatine kinase.

\(^a\) Expressed as percent of mean/median value of control group.

\(^b\) CoQ10 treatment response: (+) = mild subjective improvement; (++) = notable or significant functional improvement.

\(^c\) Ages unspecified.

\(^d\) Value based upon the mean or midpoint (if mean not specified) of the cited muscle CoQ10 reference range.

\(^e\) Improvement noted in only five patients.

\(^f\) Abnormal ETC enzymes in only two patients.

\(^g\) Patients without biochemical and histological evidence of respiratory chain disease.

\(^h\) CoQ10 effective alone, but optimal effect achieved with addition of riboflavin to CoQ10.
4.3. Challenges in the diagnosis of pediatric mitochondrial disorders

Clinical manifestations of mitochondrial diseases affecting skeletal muscle in children are variable, ambiguous, and range from hypotonia, progressive weakness, and muscle atrophy to myalgia, exercise intolerance, and recurrent rhabdomyolysis (von Kleist-Retzow et al., 2003; Munnich and Rustin, 2001; Oglesbee et al., 2006; Finsterer, 2006). Additional ambiguity arises because the vast majority of pediatric patients with mitochondrial disorders does not present as a classical syndrome, and may have non-specific features (Tsao et al., 2000; Rutledge and Finn, 2004). Genetic heterogeneity has also added to the complexity and difficulties of diagnosing mitochondrial diseases (DiMauro and Davidzon, 2005; Finsterer, 2006; McFarland et al., 2007). Scaglia et al. (2004) studied the clinical spectrum, morbidity, and mortality of 113 children with mitochondrial disease, and concluded that there is no gold standard to establish the diagnosis of mitochondrial encephalomyopathy.

Biochemical defects in the enzyme complexes of the mitochondrial respiratory chain are commonly associated with mitochondrial diseases (DiMauro, 2006). Most agree that biochemical analysis of mitochondrial ETC complex enzymes in affected muscle is an important component in the diagnostic workup, although there are many limitations to this methodology (Walker et al., 1996; Bernier et al., 2002; Oglesbee et al., 2006; Land et al., 2007). Problems with biochemical ETC complex testing include non-standardized laboratory methods, inter-laboratory variability, poorly defined cutoff values for abnormality, inadequate control groups, and deleterious effects of freezing and processing procedures on ETC enzyme activities (Munnich and Rustin, 2001; Taylor et al., 2004; Casademont et al., 2004; Gellerich et al., 2004; Hui et al., 2006; McFarland et al., 2007). In addition, mitochondrial ETC enzyme testing has been associated with false-positive (Vallance, 2004; Jongpiputvanich et al., 2005; Hui et al., 2006; Lee et al., 2007) and false-negative (Oglesbee et al., 2006) test results.

4.4. Pathology issues associated with coenzyme Q10 deficiency in skeletal muscle

For several reasons children are generally considered to be more difficult to diagnose with mitochondrial disorders than adults (Taylor et al., 2004). Issues of testing sensitivity and specificity may contribute to this problem (Bourgeois and Tarnopolsky, 2004). As noted earlier children are less likely than adults to present with a classical clinical syndrome (Taylor et al., 2004). Muscle biopsies of children with mitochondrial diseases may be normal histologically (Bourgeois and Tarnopolsky, 2004), whereas >2% RRF in muscle of adults is defined as a major diagnostic criterion for ETC disorders (Bernier et al., 2002). RRF, RBF, and COX-negative myofibers are uncommonly observed in muscle biopsies of children with suspected mitochondrial diseases (Uusimaa et al., 2000; Bernier et al., 2002; Scaglia et al., 2004; Miles et al., 2005). The current study results concur with these observations in that no study biopsies revealed RRF, RBF, or COX-negative myofibers on pathological examination.

Accumulations of mitochondria, i.e. indicated by increased staining for SDH in subsarcolemmal regions of myofibers, have been suggested as an abnormal histological finding which is associated with mitochondrial diseases. Bernier et al. added >2% SSMA as a minor criterion for diagnosis of mitochondrial diseases in children (Bernier et al., 2002). However, the adequacy of this criterion has been questioned because of the non-specificity of SSMA for mitochondrialopathy and ETC defects (Rollins et al., 2001; Patterson, 2004; Miles et al., 2005; Miles et al., 2006). A positive correlation between SSMA (%) and muscle coenzyme Q10 content was described previously by several of the current authors in a separate group of muscle biopsies from 47 children who underwent pathological evaluation (Miles et al., 2005). Only 3 of the 47 participants in that study had evidence of low ETC complex activity (Miles et al., 2005). Others have documented the proliferation of subsarcolemmal mitochondria in muscle biopsies of endurance athletes, which also supports the non-specificity of this finding (Bourgeois and Tarnopolsky, 2004). The current report provides further data which question whether >2% SSMA is an appropriate minor criterion for the diagnosis of mitochondrial diseases in children. Further investigation and clarification of this controversy is needed.

4.5. Recent advances in understanding of muscle coenzyme Q10 deficiency

Although an association between muscle coenzyme Q10 deficiency and ETC complex deficiency was reported over 15 years ago (Fischer et al., 1986; Zierz et al., 1989; Matsuoka et al., 1991), quantitative studies of coenzyme Q10 in muscle are limited. Early reports suggested that primary coenzyme Q10 deficiency was associated with marked coenzyme Q10 depletion (Ogasahara et al., 1989; Sobreira et al., 1997; Boitier et al., 1998). It is now accepted that muscle coenzyme Q10 deficiency is associated with wide variability in age, myofiber pathology, and coenzyme Q10 content (Table 5). It should be noted that one of the most consistent findings of these reports, which is similar to the current results, is the association of coenzyme Q10 deficiency with deficiencies of the ETC I + III and/or II + III complexes (Table 5).

While direct measurement of muscle coenzyme Q10 content is widely accepted to confirm the presence of coenzyme Q10 deficiency (Ogasahara et al., 1989; Sobreira et al., 1997; Boitier et al., 1998; Di Giovanni et al., 2001; Musumeci et al., 2001; Rahman et al., 2001; Van Maldergem et al., 2002; Lamperti et al., 2003; Aure et al., 2004; Gironi et al., 2004; Lalani et al., 2005; Salvati et al., 2005; Artuch et al., 2006; Horvath et al., 2006; Quinzii et al., 2006; López et al., 2007).
et al., 2006; Le Ber et al., 2007; Gempel et al., 2007), few have advocated routine quantitative evaluation of muscle coenzyme Q10 (Lamperti et al., 2003; Taylor et al., 2004; Lalani et al., 2005; Miles et al., 2005). Analytical complexity, lack of validated methods, and inadequate guidelines for interpretation of laboratory results may have limited the development of direct muscle coenzyme Q10 measurement in the past. With the recent identification of gene mutations in the biosynthetic pathway for coenzyme Q10, proof of the existence of primary coenzyme Q10 deficiency (Quinzii et al., 2006; López et al., 2006; Mollet et al., 2007), and evidence of a marked clinical response to coenzyme Q10 supplementation in some patients (Table 5), there is growing urgency to diagnose muscle coenzyme Q10 deficiency earlier in the clinical course rather than later (Musumeci et al., 2001; Di Giovanni et al., 2001; Gironi et al., 2004; Scaglia et al., 2004; Lalani et al., 2005; Salvati et al., 2005; Artuch et al., 2006; Finsterer, 2006; Dimauro and Mancuso, 2007b). The HPLC method for muscle coenzyme Q10 analysis in the current study has been described in detail elsewhere (Tang et al., 2004), and has been validated in children by the current authors (Miles et al., 2005) and in rat by others (Galinier et al., 2004).

Recently Dr. F.L. Crane, the discoverer of ubiquinone, indicated that a more readily available clinical assay for tissue coenzyme Q10 is needed because of our limited understanding of the extent and variability of this factor (Crane, 2007). Additionally the importance of direct quantitation of muscle coenzyme Q10 content has been emphasized by others (Taylor et al., 2004; DiMauro, 2006; Rötig et al., 2007). Although a definitive cutoff value for primary coenzyme Q10 deficiency has not been established, some have arbitrarily suggested that coenzyme Q10 deficiency may exist when muscle content is <50% of the mean control value (Ogashahara et al., 1989; Sobreira et al., 1997; Boitier et al., 1998; Di Giovanni et al., 2001; Lalani et al., 2005; Salvati et al., 2005; Horvath et al., 2006). Others reported markedly decreased muscle coenzyme Q10 in 13 patients, including four adults and nine children, with a cutoff value <15 μmol/g wet tissue (Lamperti et al., 2003). Their cutoff value was based upon the maximum concentration, i.e. 14.8 μmol/g tissue, observed in one of the 13 patients with genetically undefined cerebellar ataxia (Lamperti et al., 2003). Using a value 2 SD below their mean control value, Gironi et al. (2004) suggested a cutoff for primary muscle coenzyme Q10 deficiency as 15 μg/g of fresh tissue. In yet another report muscle coenzyme Q10 deficiency was suggested at 56 nmol/g protein in a 12-year-old girl with ataxia and cerebellar atrophy (Artuch et al., 2006). Obviously, differences in units of measurement and cutoff values are confusing and provide little assistance for defining a muscle coenzyme Q10 abnormality. The current authors propose that standardizing quantitative methods and guidelines for interpretation of muscle coenzyme Q10 content would facilitate the early diagnosis of muscle coenzyme Q10 deficiency, and would be particularly beneficial for pediatric patient populations.

4.6. The future of muscle coenzyme Q10 analysis

Direct measure of muscle coenzyme Q10 may provide certain advantages. For example, direct coenzyme Q10 measurement can be made on a very small muscle specimen, i.e. 20–40 mg, which may be obtained by a less invasive needle biopsy (Miles et al., 2005). In order to test the activities of a panel of ETC complex enzymes, most laboratories generally require 100–200 mg of muscle tissue. Patients must undergo a surgical procedure, i.e. an open muscle biopsy, in order to obtain this quantity of muscle. Because of the invasiveness and added expense of this surgical procedure, many families may decide to postpone the open biopsy. While not replacing ETC complex biochemical testing a needle biopsy to obtain a muscle coenzyme Q10 level may be more acceptable in the early evaluation of some children with suspected mitochondrial diseases. Obviously determination of muscle total coenzyme Q10 content should be considered essential for confirmation in any patient with a suspected primary or secondary coenzyme Q10 deficiency state.

It should also be noted that total coenzyme Q10 content of muscle is not significantly changed by freeze–thaw effects (Tang et al., 2004), whereas ETC complex activities in muscle are very susceptible to the effects of improper collection, storage, and freezing (Janssen et al., 2003; Gellerich et al., 2004). We would propose that muscle total coenzyme Q10 testing may facilitate the diagnosis and early treatment of patients with suspected muscle coenzyme Q10 deficiency.

5. Conclusion

Muscle coenzyme Q10 analysis may assist clinicians in the decision process for diagnosis and treatment of mitochondrial diseases in children. Determination that muscle coenzyme Q10 is >185 nmol/g protein significantly decreases the likelihood of a complex I + III or II + III defect. It should be noted, however, that the relationship of this cutoff value with other ETC complex deficiencies requires further investigation. If the muscle coenzyme Q10 content is below the suggested reference interval, i.e. <107 nmol/g protein, molecular investigation of a primary or secondary genetic cause of coenzyme Q10 deficiency would seem to be indicated. Evidence of a muscle coenzyme Q10 deficiency should encourage earlier supplementation with this agent.

References


