

Coenzyme Q₁₀-Responsive Ataxia: 2-Year-Treatment Follow-up

Merce Pineda, MD, PhD,^{1,2} Raquel Montero, PhD,^{2,3} Asuncion Aracil, MD,^{1,2}
Mar M. O'Callaghan, MD,^{1,2} Ana Mas, MD,⁴ Carmen Espinos, PhD,²
Dolores Martinez-Rubio, BS,^{2,5} Francesc Palau, MD, PhD,^{2,5} Placido Navas, PhD,^{2,6}
Paz Briones, PhD,^{2,7} and Rafael Artuch, MD, PhD,^{2,3*}

¹Department of Pediatric Neurology, Hospital Sant Joan de Déu, Barcelona, Spain

²Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER), ISCIII, Spain

³Department of Clinical Biochemistry, Hospital Sant Joan de Déu, Barcelona, Spain

⁴Department of Pharmacy, Hospital Sant Joan de Déu, Barcelona, Spain

⁵Genetics and Medicine Molecular Unit, Instituto de Biomedicina de Valencia-CSIC, Valencia, Spain

⁶Centro Andaluz de Biología del Desarrollo, Universidad Pablo de Olavide, Sevilla, Spain

⁷Institut de Bioquímica Clínica, Hospital Clinic and CSIC, Barcelona, Spain

Abstract: We assessed the clinical outcome after coenzyme Q₁₀ (CoQ₁₀) therapy in 14 patients presenting ataxia classified into two groups according to CoQ₁₀ values in muscle (deficient or not). We performed an open-label prospective study: patients were evaluated clinically (international cooperative ataxia rating scale [ICARS] scale, MRI, and videotape registration) at baseline and every 6 months during a period of 2 years after CoQ₁₀ treatment (30 mg/kg/day). Patients with CoQ₁₀ deficiency showed a statistically significant reduction of ICARS scores (Wilcoxon test: $P = 0.018$) after 2 years of CoQ₁₀ treatment when compared with baseline conditions. In patients without CoQ₁₀ deficiency, no statisti-

cally significant differences were observed in total ICARS scores after therapy, although 1 patient from this group showed a remarkable clinical amelioration. Biochemical diagnosis of CoQ₁₀ deficiency was a useful tool for the selection of patients who are good candidates for treatment as all of them responded to therapy. However, the remarkable clinical response in 1 case without CoQ₁₀ deficiency highlights the importance of treatment trials for identification of patients with CoQ₁₀-responsive ataxia. © 2010 Movement Disorder Society

Key words: coenzyme Q₁₀ deficiency; mitochondrial disorders; ataxia; cerebellum; pediatric patients.

Primary coenzyme Q₁₀ (CoQ₁₀) deficiency has been described as an autosomal recessive disease with heterogeneous phenotypes; among them, cerebellar ataxia is the most frequent one.¹ Mutations in five different nuclear genes involved in CoQ₁₀ biosynthesis have been described: *COQ2* (MIM 609825),² *PDSS1* (MIM 607429),³ *PDSS2* (MIM 610564),⁴ *CABCI* (MIM 606980),^{5,6} and *COQ9* (MIM 612837) genes.⁷ Muta-

tions in *CABCI* have been associated with the ataxic form of CoQ₁₀ deficiency syndromes.

The response to replacement therapy in the ataxic form of CoQ₁₀ deficiency is variable. Some patients had good clinical outcome after CoQ₁₀ supplementation, whereas some others with genetically confirmed CoQ₁₀ deficiency showed negligible response.⁶

Our goal was to assess the clinical outcome after CoQ₁₀ therapy in 7 patients with ataxia and CoQ₁₀ deficiency in muscle and/or fibroblasts and in 7 patients with ataxia but without CoQ₁₀ deficiency.

Additional Supporting Information may be found in the online version of this article.

*Correspondence to: Dr. Rafael Artuch, Department of Clinical Biochemistry, Hospital Sant Joan de Déu, Passeig Sant Joan de Déu, 2, 08950 Esplugues, Barcelona, Spain. E-mail: rartuch@hsjdbcn.org

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METHODS

Patients

We performed an open-label prospective study. The eligible patients were those with congenital cerebellar

ataxia of unknown origin as the main symptom (9 females and 5 males; age range, 2–38 years; mean, 11 years): we excluded Friedreich ataxia, ataxia associated with vitamin E deficiency, ataxia-telangiectasia, ataxia with oculomotor apraxia, late-onset forms (spinocerebellar ataxias types 1 and 2 in a girl and her father [Cases 6 and 7]), ataxia associated with mutations in mitochondrial DNA (NARP syndrome in 4 patients from Group 2), and other known inherited forms of ataxia in basis of clinical, biochemical, and molecular genetic grounds. The main clinical features are listed in Table 1. We classified these 14 patients into two groups based on CoQ₁₀ content in muscle or fibroblasts and on mitochondrial respiratory chain enzyme activities, following previously reported criteria⁸: Group 1 included 7 patients with CoQ₁₀ deficiency in muscle (range, 1.31–2.60 nmol/citrate synthase units [mean, 1.99; standard error of the mean, 0.27]; reference values: 2.7–8.5 [mean, 5.4]). These 7 patients presented a clear reduction in the activity of CoQ₁₀-dependent mitochondrial respiratory chain enzymes, as previously reported.⁸ In all 7 patients, CoQ₁₀ deficiency was further confirmed in fibroblasts (data not shown). Group 2 included 7 patients without CoQ₁₀ deficiency in muscle (range, 2.7–6.7 nmol/citrate synthase units [mean, 4.12; standard error of the mean, 1.29]). All patients presented CoQ₁₀ values in fibroblasts related to citrate synthase in the normal range (data not shown).

Muscle CoQ₁₀ reference values were established in 37 pediatric patients, as previously reported.⁸ For fibroblasts, skin biopsies were taken from 65 patients of similar ages (2–16 years, average: 9.5) for differential diagnosis of inborn errors of metabolism: exclusion criterion was diagnosis of mitochondrial energy metabolism disorder.

The study protocol was approved by the ethics committee of the Hospital Sant Joan de Déu. Informed consent was obtained from parents and adult patients.

BIOCHEMICAL AND MOLECULAR PROCEDURES

Screening for inborn errors of metabolism, including analysis of plasma amino acids, sialotransferrin, biotinidase activity, and urine organic acids, gave normal results in all patients. Celiac disease was also routinely ruled out.

Mitochondrial respiratory chain enzyme activities were measured by spectrophotometric procedures.⁹ Muscle and fibroblast CoQ₁₀ concentrations were determined by reversed-phase high-pressure liquid chromatography (Waters, MA) with electrochemical

detection (Coulchem II, ESA, MA), as previously reported.⁹

We performed genetic analysis of five of the genes involved in the CoQ₁₀ biosynthetic pathway (*COQ2*, *PDSS1*, *PDSS2*, *CABC1*, and *COQ9*) in 6 patients belonging to Group 1 (Cases 1, 2, 3, 4, 5, and 6) by direct sequencing of each exon and their intron boundaries in an ABI Prism 3130xl autoanalyzer (Applied Biosystems, Foster City, CA).

TREATMENT PROTOCOL

The patients were evaluated clinically and biochemically at baseline and every 6 months after CoQ₁₀ administration (dodecarenone) for a period of 2 years. CoQ₁₀ dosage was chosen according to previously reported regimens¹⁰ and was the same for all patients (30 mg/kg/day orally three times per day). Patients reported in this article were treated with oral CoQ₁₀ for compassionate use. No carnitine, vitamins, or antioxidants were simultaneously applied.

Clinical Evaluation

Neurological evaluations were always performed by the same investigator. The neurological status of our 14 patients was assessed using the international cooperative ataxia rating scale (ICARS)¹¹ in which higher scores indicate a more severe disease: posture and gait (0–34 points), kinetic functions (0–52 points), dysarthria speech (0–8 points), and oculomotor movement disorders (0–6 points). We compared ICARS scores at baseline and at 6, 12, and 24 months after the initiation of therapy. We considered that the patients improved when we observed a significant reduction in posture and kinetic function scores. Video recordings of the patients were made at baseline and every 6 months after the introduction of CoQ₁₀ therapy, and cranial MRI and electroneurophysiological studies were obtained at the beginning and at the end of the study.

Biochemical Monitoring

To control CoQ₁₀ treatment compliance, EDTA blood samples were taken at baseline and every 6 months after the start of therapy. All samples were collected in the fasting state (and 10–12 hours after the last oral CoQ₁₀ doses), and plasma samples were stored at –80°C before CoQ₁₀ analysis.

TABLE 1. Clinical data for Groups 1 (CoQ₁₀-deficient Patients) and 2 (no CoQ₁₀-deficient Patients) before and after the start of the therapy

	Case	Sex/Baseline age	Clinical phenotype	Baseline ICARS	ICARS after treatment	Clinical phenotype after treatment
Group 1	Case 1	F / 6 yr	Walks with autonomous support, extremely slowly. Stands up with considerable sway. Moderate dysmetry. Mild modification fluency	34	16	Walks alone, slightly reduced speed. Stands up with no sway. Oscillating movements on finger to nose. Slight fluency
	Case 2	F / 8 yr	Walks with autonomous support, extremely slowly. Stands up with considerable sway.	25	17	Walks alone, reduced speed. Stands up with moderate sway. Slight fluency
	Case 3	F / 12 yr	Walks without support, abnormal and irregular gait. Reduced speed. Segmented dysmetric movement. Slurred speech	30	18	Walks normally at normal speed. Able to stand on one foot. Very slight oscillation movement on finger to nose. Very slight slurred speech.
	Case 4	F / 8 yr	Walks without support, abnormal and irregular gait. Markedly reduced speed. Transient nistagmus. Slight saccadic pursuit. Myoclonic epilepsy. Mental retardation	37	26	Walks almost normally. Slightly reduced speed. Same slight dysmetry and slurring of speech. No nystagmus with normal pursuit. Myoclonic epilepsy. Mental retardation
	Case 5	F / 12 yr	Unable to walk in tandem, slightly reduced speed. Oscillation movement. Without decomposition on finger to nose. Slurred speech	10	2	Normal walking and fine tremor. Normal speed. Normal speech
	Case 6	M / 13 yr	Walks without support, abnormal and irregular gait. Oscillation movement without decomposition on finger to nose. Moderate modification of fluency. Suggestive slurring	19	2	Normal walking. Mild instability on finger-finger. Mild modification of fluency.
	Case 7	M / 38 yr	Slight action tremor. Mild modification of fluency. Transient nystagmus. Slight saccadic pursuit	5	2	No tremor. Normal fluency of speech. Same nystagmus and saccadic pursuit
Group 2	Case 8	F / 2 yr	Walks without support, abnormal and irregular gait. Reduced speed. Oscillating mild instability on finger-finger, irregular and slow movements. Moderate fluency	12	16	Walks without support, abnormal and irregular. Normal speed. Oscillating mild instability on finger-finger, irregular and slow movements. Mild fluency
	Case 9	F / 21 yr	Walks without support, abnormal and irregular gait. Markedly reduced speed, no tandem position. Moderate dysmetry. Mild fluency and slurring of speech. Moderate nystagmus. Slight saccadic movement	23	16	Walks without support, abnormal and irregular. No tandem position. Same dysmetry and speech. Moderate nystagmus, no saccadic movements
	Case 10	M / 4 yr	Walks without support with considerable staggering. Extremely slow. Instability and oscillating movements finger to nose. Mild fluency	31	25	Walks without support without staggering. Oscillating movements finger to nose. Same speech
	Case 11	F / 17 yr	Almost normal walking. Moderate tremor, dysmetry. Myoclonus and mental retardation. Oculomotor apraxia	29	31	Almost normal walking. Less tremor, slight dysmetry. Myoclonus and mental retardation. Oculomotor apraxia
	Case 12	M / 18 yr	Walks without support, abnormal and irregular gait. Body sway with moderate oscillations. Dysmetry, tremor. Transient nystagmus. Mental retardation	28	30	Walks without support: slow, abnormal, and irregular. Body sway with moderate oscillations. Dysmetry, tremor. Transient nystagmus. Less fluency. Mental retardation
	Case 13	F / 7 yr	Walks without support, abnormal and irregular, reduced speed. Oscillating movements, instability. Normal speech	14	12	Almost normal walking, normal speed. Oscillating movements with slight instability.
	Case 14	M / 4 yr	Almost normal walking, slight reduced speed. Oscillating movements, mild instability. Suggestion of slurred speech	16	7	Almost normal walking with normal speed, with occasional Oscillating movements. Slight modification fluency of speech.

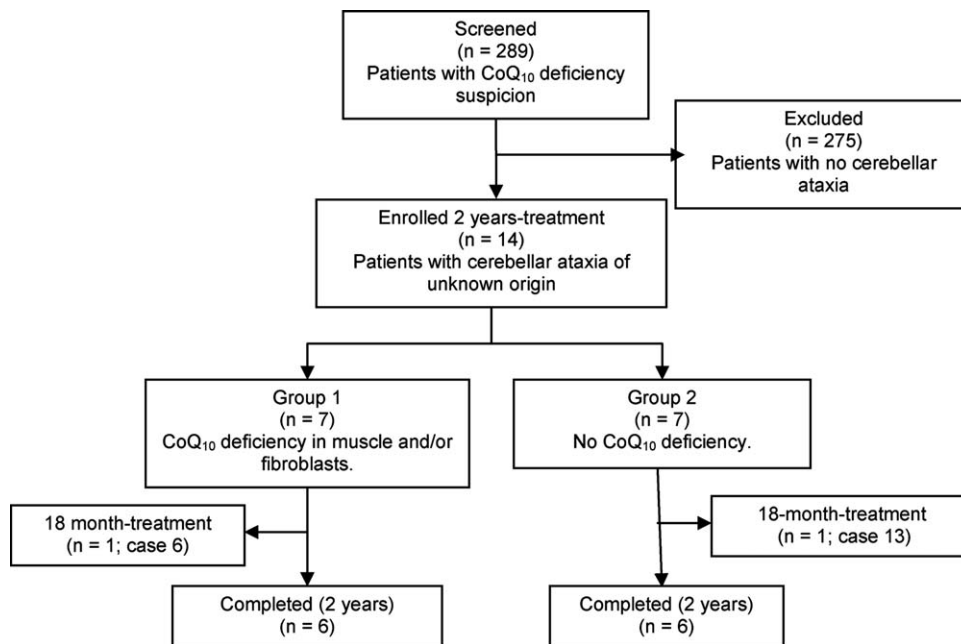


FIG. 1. Patient flow diagram.

Statistical Analysis.

Mann-Whitney U and Student's *t* tests were applied to compare ICARS scores, plasma CoQ₁₀ levels, and ages between Groups 1 and 2, and the Wilcoxon test was used to compare paired ICARS score data before the start of the therapy and at 6, 12, and 24 months after therapy. Statistical significance was considered as $P < 0.05$. Calculations were performed with the SPSS 17.0 program.

RESULTS

All patients enrolled in this study completed the period established for CoQ₁₀ treatment, except for patients 6 and 13 who are still being followed-up (18-month period; Fig. 1), as they were enrolled 1 year later. No putative side effects were observed during the duration of CoQ₁₀ therapy in any case.

Mutational screening of the *COQ2*, *PDSS1*, *PDSS2*, *CABC1*, and *COQ9* genes only revealed a single base change in the *CABC1* gene in Patient 2 who was heterozygous carrier for the c.1825C>G (p.L609V) mutation in exon 15. *CABC1* cDNA from this case was analyzed for the presence of large deletions, and no change was found.

Total ICARS, posture and gait, kinetic function scores, and the ages of Group 1 and 2 patients are

reported in Table 2. No statistically significant differences were observed when we compared total ICARS, posture and gait, kinetic function scores, and age between the two groups at baseline.

Clinical data and results of ICARS scores of patients at the beginning and after CoQ₁₀ treatment are presented in Table 1 and Figure 2. All Group 1 cases showed an improvement in total ICARS scores after 24 months of therapy (Table 1; Fig. 2). These patients showed a statistically significant reduction of ICARS (in total values Wilcoxon test: $P = 0.018$), posture and gait ($P = 0.017$), and kinetic function scores ($P = 0.043$) when they were compared at baseline and after 2 years of CoQ₁₀ treatment. In baseline conditions, oculomotor disorders were limited to nystagmus in 2 of 7 patients and abnormal ocular pursuit in 1 patient. In Group 2, the ICARS scale evaluation after CoQ₁₀ therapy showed that Case 14 clearly improved, 3 patients showed slight improvement, and 3 worsened. However, for the group as a whole, there were no statistically significant differences either in total ICARS ($P = 0.396$) or in kinetic function and posture and gait scores between patients and between baseline and after 24 months of CoQ₁₀ therapy (Table 2; Fig. 2).

Considering patients individually, Cases 5, 6, and 14 showed the best clinical response. The videotapes show Patient 6 at baseline and at the end of the investigation. There was a clear improvement in kinetic

TABLE 2. Age at the start of therapy and ICARS scores in baseline conditions and after 24 months of CoQ₁₀ treatment in patients from Groups 1 and 2

	Age	ICARS (baseline)	ICARS (end of treatment)	Posture (baseline)	Posture (end of treatment)	Kinetic function (baseline)	Kinetic function (end of treatment)
Group 1	(6–38) 13.8 ± 4.1	(4.5–37) 22.5 ± 4.6	(1.5–26) 11.6 ± 3.7	(0.5–16.5) 8.8 ± 2.3	(0–9) 3.3 ± 1.4	(1–18) 10.4 ± 2.6	(1–16) 6.6 ± 2.2
Group 2	(2–21) 10.1 ± 3.1	(12–31) 21.6 ± 2.9	(7–31) 19.3 ± 3.4	(0.5–14) 7.5 ± 1.6	(2–13) 6.5 ± 1.5	(4–26) 10.8 ± 2.9	(2.5–20) 8.8 ± 2.3

Results are expressed as range, mean, and standard error of the mean.

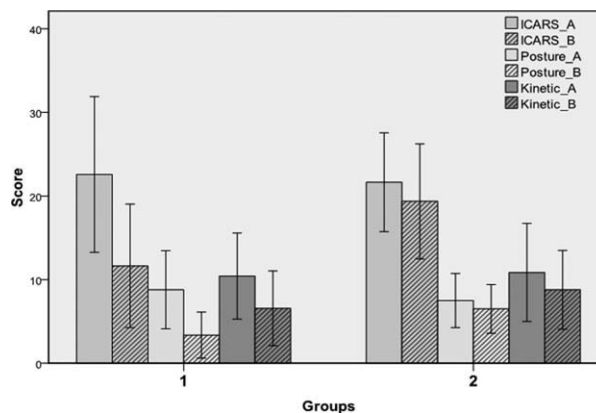


FIG. 2. Total ICARS, posture and kinetic function scores for Groups 1 and 2. Point A: baseline conditions and Point B: 2 years after CoQ₁₀ treatment. Data are expressed as mean (columns) and standard error of the mean (bars).

functions (Video 1, Supporting Information) and in gait and posture (Video 2, Supporting Information). For Case 2, the patient with a nucleotide change in *CACB1* gene did not show a clear response to the treatment. Conversely, Case 14, with no CoQ₁₀ deficiency, showed a remarkable reduction in ICARS score (from 16 to 7 points).

Regarding CoQ₁₀ monitoring, plasma values at baseline ranged from 0.33 to 1 μmol/L (reference values: 0.41–1.15 μmol/L) and increased after supplementation in all patients, confirming that all of them had good treatment compliance. No significant differences were observed in mean plasma CoQ₁₀ concentrations after the start of therapy between Group 1 (range, 3.1–13.6; average, 8.8 μmol/L) and Group 2 (range, 4.8–13.3; average, 8.3 μmol/L).

Neurophysiological studies did not show neuropathic or myopathic patterns in any patient before the start of therapy. In Group 1, MRI evidenced cerebellar atrophy in all patients, in 4 of whom (Cases 2, 3, 5, and 7) the atrophy was severe. In Case 2, the very pronounced cerebellar atrophy observed at the start of the therapy did not change noticeably after 1 year on CoQ₁₀. Case 6, who had a remarkable clinical response to therapy, showed only moderate cerebellar atrophy with vermian involvement. In Group 2, only 2 of 7 patients showed cerebellar atrophy, whereas in the other 5 (Cases 8, 11, 12, 13, and 14), the MRI was normal or revealed only slight atrophy. Case 14 had a normal MRI.

DISCUSSION

The ataxic form is the most common of the CoQ₁₀ deficiency syndromes.¹² To our knowledge, no studies

have reported long-term follow-up of these patients after CoQ₁₀ supplementation.

According to several authors, the response to treatment in CoQ₁₀ deficiency patients with ataxia is usually good but variable.^{1,6} As no agreement on CoQ₁₀ dosage exists at present, we established a 30 mg/kg/day regimen following previously reported experiments.¹⁰ This dose proved to be effective as patients presented a positive clinical outcome (Fig. 2).

In all our patients from Group 1, neurological outcome based on ICARS scale after CoQ₁₀ therapy was good, especially for posture and gait scores (all patients had low scores in this subtest). Although statistically significant improvement was observed for kinetic function, 5 of 7 patients improved in this subtest but 2 remained stable. Interestingly, the only case with a proven mutation in *CABC1* did not respond any better than other patients with no mutations in the genes we screened for. The severe cerebellar involvement in this case may explain this moderate response. This is not too surprising as there are descriptions of other patients with ataxia and CoQ₁₀ deficiency who showed no clinical improvement after treatment.⁶

The response to treatment of Group 2 was more variable, ranging from good in 1 case to none or worsening in others. As recently described, the CoQ₁₀ amount in patients carrying mutations at *CABC1* gene may be only mildly decreased in muscle and normal in fibroblasts.^{5,6} Therefore, it seems prudent to sequence this gene in patients with ataxia of unknown origin and with good clinical outcome after CoQ₁₀ supplementation. Moreover, these observations outline the importance of improving the biochemical tools to detect patients with CoQ₁₀ deficiency for therapeutical trials.

Some variables may influence the ICARS score evolution after CoQ₁₀ or other therapies, such as the age of patients at the start of the therapy, the severity of the disease (evaluated as total ICARS score), treatment compliance, training, and physiotherapy.^{13,14} Our results showed no statistically significant differences in ICARS scores or patient age between Groups 1 and 2 at the start of the therapy, suggesting that these variables did not explain the different clinical outcomes. Nor did treatment compliance differ between the two groups, according to plasma CoQ₁₀ values. Concerning physiotherapy, only 3 patients from Group 2 were under this treatment concomitantly to CoQ₁₀ therapy. This fact might, as previously suggested,¹⁴ explain the improvement observed in Cases 10 and 14 belonging to Group 2. The influence of other factors, such as spontaneous improvement, is difficult to rule out, although a very remarkable amelioration was noticed in patients after CoQ treatment when

compared with the evolution of the previous years with no CoQ therapy.

Cerebellar atrophy has been related with the ataxic forms of CoQ₁₀ deficiency,⁶ although no MRI studies in large series are available for these patients. According to our results, MRI alterations in Group 1 were considerably more severe than in Group 2. Interestingly, Case 6, who showed only a mild vermian atrophy, had the best clinical response among all patients (Videotape). The normal MRI in Case 14 may correlate with his very good clinical response.

Concerning genetic studies, only Case 2 harbored a heterozygous nucleotide change in *CABC1* gene, but we failed to detect any other change in patients. Therefore, in all likelihood, other genes are associated with the ataxic form of CoQ₁₀ deficiency syndromes, but they remain to be identified.

In conclusion, in the absence of a reliable molecular diagnosis of CoQ₁₀ deficiency, biochemical diagnosis was useful in selecting patients for CoQ₁₀ supplementation as all of them responded well to treatment. Furthermore, the remarkable clinical response in 1 patient with no CoQ₁₀ deficiency in fibroblasts or muscle and the previous observation that some patients may present mutations in *CABC1* gene without CoQ₁₀ deficiency highlight the importance of treatment trials for the identification of patients with CoQ₁₀-responsive ataxia.

LEGENDS TO THE VIDEO

Video 1. Posture and gait evaluation of Case 6 at the start of CoQ₁₀ therapy (first part of the video) and after 1 year of CoQ therapy. Gait in tandem position clearly improved.

Video 2. Kinetic function evaluation of Case 6 at the start of CoQ₁₀ therapy (first part of the video) and after 1 year of CoQ therapy. Fine motor skills improved, and it is noteworthy that the patient recovered facial expression after therapy.

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