LETTER TO THE EDITOR

Expanding the clinical spectrum of primary coenzyme Q10 deficiency type 6: The first case with cardiomyopathy

Primary coenzyme Q10 deficiency (primary COQ10 deficiency) is a rare mitochondrial respiratory chain disease caused by biallelic variants in: COQ2, COQ4, COQ6, COQ7, COQ8A, COQ8B, COQ9, PDSS1, or PDSS2. The clinical manifestations and age at onset are highly variable. Primary COQ10 deficiency type 6 (primary COQ10 deficiency-6, MIM#614650), caused by biallelic variants in COQ6, is characterized by steroid-resistant nephrotic syndrome and sensorineural deafness.

Here, we report a 19-month-old female patient with an unusual presentation. She was born term with a normal birth weight to Lebanese consanguineous parents (Figure 1A). At age 19 months, she was admitted with a respiratory tract infection caused by a rhinovirus. One day after admission, she had an in-hospital cardiorespiratory arrest and was successfully resuscitated after 10–15 min. Echocardiogram showed an impaired systolic function, dilatation of the left ventricle and mild left ventricular hypertrophy without structural abnormalities (Figure 1B,C). Additionally, she had proteinuria (0.44 g/L; albuminuria: 224 mg/L) and borderline microcephaly (43.5 cm; −2.70 SDS). Retrospectively, her motor development was mildly delayed (walking supported: 12–13 months; walking unaided: not achieved), and parents reported muscle weakness in the upper legs. She was treated with vasoactive and cardiotonic drugs (noradrenaline, norepinephrine).
Its deleterious effect is validated by functional studies in yeast.

Primary COQ10 deficiency-6 has previously been reported in 31 patients. Steroid-resistant nephrotic syndrome and/or sensorineural deafness are often the initial manifestations. To date, a cardiac phenotype has been reported in four patients with primary COQ10 deficiency-6. Three patients had a structural heart disease (tetralogy of Fallot; atrial septal defect with persistent left superior vena cava) and one had cardiovascular abnormalities not further specified. Cardiomyopathy has not been described yet. This report expands the phenotypic spectrum of primary COQ10 deficiency-6.

Although not reported in primary COQ10 deficiency-6, cardiomyopathy has been described in 26 patients with primary COQ10 deficiency. Hypertrophic cardiomyopathy is the most common type of cardiomyopathy (17/26). Five patients had dilated cardiomyopathy. The mortality among patients with a cardiomyopathy is high: 18/26 (70%). Five patients died ≤2 years of age. Post-mortem examination of cardiac tissue was performed in seven cases. Most showed nonspecific changes of cardiomyocyte hypertrophy.

Disease progression may be limited by COQ10 supplementation, however the response to treatment is highly variable. In most patients with cardiomyopathy COQ10 treatment was not effective. However, cardiac function improved in two patients with biallelic variants in COQ4 and COQ7 and stabilized in two other patients with biallelic variants in COQ4 after COQ10 supplementation. COQ10 supplementation was not started in our patient because primary COQ10 deficiency was not initially suspected and the genetic test results only became available after she died.

In conclusion, we describe a case of cardiomyopathy in primary COQ10 deficiency-6, which expands the phenotypic spectrum. It underscores the importance of cardiac evaluation in these patients. Genetic testing for primary COQ10 deficiency, including COQ6, should be considered in patients with pediatric-onset cardiomyopathy as it can guide treatment options. Additionally, it can help to identify relatives at risk and it can be of importance for reproductive choices.

ACKNOWLEDGMENTS
We are grateful for the participation of the patient’s parents. We thank Kate McIntyre for editorial advice.

CONFLICT OF INTEREST
The authors have no conflict of interest to disclose.

PEER REVIEW
The peer review history for this article is available at https://publons.com/publon/10.1111/cge.14182.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT
Written informed consent was obtained.

Lisette Leeuwen, Charlotte M. A. Lubout, Hessel P. Nijenhuis, Linda C. Meiners, Yvonne J. Vos, and Johanna C. Herkert
department of Genetics, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
Department of Pediatrics, Section of Metabolic Diseases, University of Groningen, Groningen, The Netherlands
Department of Pediatrics, Center for Congenital Heart Diseases, University of Groningen, Groningen, The Netherlands
Department of Radiology, University of Groningen, Groningen, The Netherlands

Correspondence
Johanna C. Herkert, Department of Genetics, University Medical Center Groningen, P.O. Box 30.001, 9700RB Groningen, The Netherlands. Email: j.c.herkert@umcg.nl

ORCID
Lisette Leeuwen https://orcid.org/0000-0002-1105-0455
Johanna C. Herkert https://orcid.org/0000-0003-0461-9102

REFERENCES