Distal phalangeal erythema in an infant with biallelic PDSS1 mutations: Expanding the phenotype of primary Coenzyme Q₁₀ deficiency

Marcello Bellusci¹,²,³ | Maria Teresa García-Silva¹,²,³
Ana Martínez de Aragón⁴ | Miguel Angel Martín²,³

¹Reference Center for Inherited Metabolic Disorders, MetabERN Center, “12 de Octubre” University Hospital, Madrid, Spain
²Mitochondrial & Neuromuscular Disorders Research Group, Instituto de Investigación Sanitaria “12 de Octubre” (imas12), Madrid, Spain
³Spanish Biomedical Research Networking Center in Rare Diseases (CIBERER), Madrid, Spain
⁴Pediatric Neuroradiology, “12 de Octubre” University Hospital, Madrid, Spain

Correspondence
Marcello Bellusci, Reference center for Inherited Metabolic Disorders, Hospital Universitario 12 de Octubre, Av/Cordoba s/n 28041, Madrid, Spain.
Email: marcello.bellusci@salud.madrid.org

Abstract
We report a detailed clinical examination in a patient with primary coenzyme Q₁₀ deficiency caused by biallelic mutations in the PDSS1 gene who presented clinical features of mitochondrial encephalopathy associated with pulmonary hypertension, livedo reticularis and particularly, chronic distal phalangeal erythema. Laboratory testing showed elevated plasma lactate and 3-methyl-glutaconic and tricarboxylic aciduria. Supplementation with high dose of coenzyme Q₁₀ was not effective to control disease progression and the patient died at the age of 3 years old because of a progressive multisystem disorder. Cutaneous involvement in mitochondrial disease is heterogenous, including proliferative, inflammatory, and dystrophic changes among others. The coexistence in our case of phalangeal erythema, livedo reticularis, and pulmonary hypertension suggests microvascular dysfunction as a possible underlying mechanism. This is the first reported patient with PDSS1 mutations presenting with 3-methyl-glutaconic aciduria and distal phalangeal erythema, expanding the phenotype of primary coenzyme Q₁₀ deficiency.

Keywords
coenzyme Q₁₀, cutaneous, phalangeal, erythema, mitochondria, PDSS1

We report the detailed clinical examination of an infant with primary coenzyme Q₁₀ (CoQ₁₀) deficiency, previously published in a case series,¹ presenting unusual finger findings.

He was born prematurely after in vitro fertilization pregnancy, complicated by twin-twin transfusion.

At the age of 5 months, he presented failure to thrive, hypotonia, feeding difficulties, bilateral hearing impairment, pulmonary hypertension, livedo reticularis, and distal phalangeal erythema (Figure 1). Laboratory tests showed anemia, lactic acidosis, 3-methyl-glutaconic, and tricarboxylic aciduria and decreased CoQ₁₀ levels in lymphocytes. At this time, oral ubidecarenone was started at 15 mg/kg/day. Three months later, when biallelic PDSS1 mutations were identified (NM_014317.3: c.716 T > G (p.Val239Gly) and NM_014317.3: c.1183C > T (p.Arg395*)), ubidecarenone was increased to 30 mg/kg/day.

However, he developed a progressive multisystem disorder with severe developmental delay, pyramidal dysfunction, seizures, tremor, optic atrophy and nystagmus, severe visual and hearing impairment, white matter cystic change and chronic heart failure. He died at the age of 3 years old.

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Since the age of 5 months, distal phalangeal erythema was an accompanying sign. Cutaneous involvement in mitochondrial disease is heterogenous, including proliferative, inflammatory, and dystrophic changes among others. The coexistence in our case of phalangeal erythema, livedo reticularis, and pulmonary hypertension suggests microvascular dysfunction as a possible underlying physiopathogenic mechanism. Symptoms related to microvascular dysfunction and cutaneous involvement have been previously reported in primary CoQ10 deficiencies, (eg, livedo reticularis and pulmonary hypertension in PDSS1, acrocyanosis in COQ4, and lupus-like symptoms in CoQ8A). In conclusion, our data expand the phenotypic spectrum associated with PDSS1 variants and primary coenzyme Q10 deficiency.

CONFLICT OF INTEREST
Marcello Bellusci, Maria Teresa García-Silva, Ana Martínez de Aragón, and Miguel Angel Martín declare that they have no conflict of interest.

AUTHOR CONTRIBUTION
Marcello Bellusci and Maria Teresa García-Silva are the clinician who attended the reported patient, planned, wrote and revisited critically the article before the submission. Ana Martínez de Aragón is the pediatric radiologist that realized the reported brain MRI studies, wrote the figure legend and revisited critically the article before the submission. Miguel Angel Martín performed and analyzed laboratory tests, revisited critically the article before the submission.

INFORMED CONSENT
All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study, including for the use of pictures.

ETHICS APPROVAL
No ethics approval is required for case report in our center.

ORCID
Marcello Bellusci https://orcid.org/0000-0003-0498-9787
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How to cite this article: Bellusci M, García-Silva MT, Martínez de Aragón A, Martín MA. Distal phalangeal erythema in an infant with biallelic PDSS1 mutations: Expanding the phenotype of primary Coenzyme Q10 deficiency. JIMD Reports. 2021;62:3–5. https://doi.org/10.1002/jmd2.12216