Intrafamilial Variability in *LPIN1*-Related Rhabdomyolysis

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Established Facts

- *LPIN1* molecular alterations are a major cause of severe recurrent rhabdomyolysis.
- The prognosis is poor, with a third of patients dying from cardiac arrest during an acute episode.

Novel Insights

- Here, we describe the first patient harbouring biallelic mutations in *LPIN1* and only presenting with a mild phenotype.
- This report expands the phenotypic spectrum of *LPIN1*-related rhabdomyolysis, illustrating high intrafamilial variability.

Keywords

Intrafamilial variability · *LPIN1* · Next-generation sequencing · Rhabdomyolysis

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Abstract

LPIN1 molecular alterations were identified as a major cause of severe recurrent rhabdomyolysis. The prognosis is poor, with a third of patients dying from cardiac arrest during an acute episode. We describe herein a familial case of a young boy and his mother both affected by the same homozygous *LPIN1* mutation. The index case experienced a first extremely severe episode of rhabdomyolysis at 14 months of age (creatinine kinase 630,000 UI/L) and a second, lethal episode

at 3 years of age. His mother had only 1 moderate episode of rhabdomyolysis (creatinine kinase 3,050 UI/L) in adulthood. Several cases of sudden death were also reported in the family. To the best of our knowledge, the mother of the index case is, to date, the first patient described harbouring biallelic mutations in *LPIN1* and only presenting with a mild phenotype. This report expands the phenotypic spectrum of *LPIN1*-related rhabdomyolysis, illustrating high intrafamilial variability.

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Rhabdomyolysis is a clinical emergency characterised by fulminant skeletal muscle damage and release of intracellular muscle components. Rhabdomyolysis can result in myoglobinuria, acute renal failure, and cardiac arrhythmia. Causes are multiple, ranging from acquired conditions such as trauma, intoxication or infection, to inherited muscle disorders including primary fatty acid oxidation disorders [Scalco et al., 2015]. *LPIN1* (OMIM 605518) molecular alterations were identified as a major cause of severe recurrent rhabdomyolysis, mostly triggered by febrile illnesses, usually beginning in early childhood [Michot et al., 2010, 2012; Jaradat et al., 2016]. Since the first report [Zeharia et al., 2008], more than 50 patients have been described. *LPIN1* is located in 2p25.1, spans 19 exons, and encodes an 890 amino acid protein, lipin-1, predominantly expressed in skeletal muscle and adipose tissue. Lipin-1 is involved in lipid biosynthesis and transcriptional regulation. Constitutive impairment of lipid metabolism and its exacerbation by proinflammatory cytokines may lead to metabolic decompensation and rhabdomyolysis [Michot et al., 2013; Hamel et al., 2015; Schweitzer et al., 2015]. Recently, Nunes et al. [2016] compiled the 36 *LPIN1* mutations reported to be related to rhabdomyolysis. Mutations are mostly missense and scattered throughout the *LPIN1* coding region with no mutational hotspot. The intragenic deletion of exons 18 and 19

(p.Glu766_Ser838del) is recurrent in Caucasian patients, suggesting a founder effect in this population [Michot et al., 2010]. Prognosis is poor, with a third of patients dying from cardiac arrest during an acute episode [Bergounioux et al., 2012; Legendre et al., 2018]. Active management of rhabdomyolysis episodes is necessary in paediatric intensive care units with therapeutic approaches including hydration, electrolyte replacement, high-calorie intake, and corticosteroids [Meijer et al., 2015; Pichler et al., 2015]. We describe herein a familial case of a young boy and his mother both affected by homozygous *LPIN1*-related rhabdomyolysis with high intrafamilial variability.

Case Report

Patient 1

The index case is a 3-year-old Comorian boy (Fig. 1, III:3). His parents were from the same small village in the Comoros without known consanguinity, and he had 2 sisters. He was born at full term with birth measurements in the average (weight: 3,410 g, length: 50 cm, head circumference: 33.5 cm), without any distress. The first months of life were uneventful. Growth was regular, and psychomotor development was within the normal range; he was able to walk unaided at 13 months of age. At 14 months of age he experienced a first extremely severe episode of acute rhabdomyolysis. During the first 48 hours, symptoms began with vomiting and profuse diarrhoea and required symptomatic treatment. At day 3, he presented to the paediatric emergency department with an acute flaccid tetraplegia with normal consciousness and overt myoglobinuria (240,000 µg/L). Initial laboratory tests found a high creatine kinase (CK) concentration (160,000 UI/L; N: <200), high aspartate aminotransferase concentration (2,300 UI/L; N: <35), high alanine aminotransferase concentration (800 UI/L; N: <35), hyperkalaemia (7 mmol/L; N: 3.4–4.7), hyponatraemia (124 mmol/L; N: 138–145), and metabolic acidosis (10 mmol/L; N: 20–28 and pH 7.24; N: 7.32–7.42); lactic acid concentration was normal. The patient was transferred to the paediatric intensive care unit. Over the following 48 hours, CK, aspartate aminotransferase, and alanine aminotransferase concentrations were markedly elevated (peak concentrations, 630,000 UI/L, 11,000 UI/L, and 6,000 UI/L, respectively). There was no liver, kidney, or cardiac failure; prothrombin time, factor V, creatinine, troponin, and cardiac ul-

Fig. 1. Family tree. The index case (III:3), homozygous for c.847dupA *LPIN1* mutation, is marked by an arrow. His homozygous mother is II:7; his heterozygous father and sister are II:6 and III:2, respectively, and his sister who suffered unexpected sudden death is III:1. The mother's 2 sisters and 2 maternal aunts who died in early infancy without any aetiological diagnosis are I:5, I:6, II:8, and II:9, respectively.

trasounds were normal. Brain tomography was normal. Electroencephalograms showed initial background slowing and were rapidly normalised. Electromyogram was purely myogenic. Wide metabolic screening was negative, except for an intense ketoacidosis on acyl-carnitine profile and urine organic-acid profile, with secondary lactic acidosis (7 mmol/L; N: <2). There was no evidence supporting an inherited fatty acid oxidation defect on acylcarnitine profile performed during acute decompensation. Norovirus I gastroenteritis was found and considered as a probable trigger. He required an initial active management of hydration and electrolytes, including intravenous sodium bicarbonate, associated with high-calorie intake and carnitine supplementation. The patient received intensive physiotherapy, and clinical recovery with CK normalisation was complete after 3 months. At 3 years of age, he experienced a second episode of rhabdomyolysis. He presented with acute flaccid tetraparesis to the paediatric emergency department, without obvious infectious cause. He did not have any muscular symptoms between the 2 attacks. In contrast to the first episode, initial laboratory tests were relatively reassuring with moderate hyperCKaemia (4,500 UI/L), high aspartate aminotransferase concentration (120 UI/L), high alanine aminotransferase concentration (45 UI/L), hyperkalaemia (5.2 mmol/L), hyponatraemia (134 mmol/L), low pH 7.22, metabolic acidosis (10 mmol/L), and lactic acidosis (6 mmol/L). The patient was transferred to the paediatric intensive care unit. Twenty minutes after admission, sudden cardiac arrest occurred on completely akinetic myocardium. Peak concentrations of CK, aspartate aminotransferase, alanine aminotransferase, lactic acid, and troponin were, 730,000 UI/L, 13,000 UI/L, 2,600 UI/L, 19 mmol/L, and 19 mmol/L (N: <2.2), respectively. The patient died from severe anoxic cerebral lesions 48 hours thereafter despite intensive management including extracorporeal membrane oxygenation and haemodialysis. Muscle biopsy and autopsy were refused.

Patient 2

The mother of the index case (Fig. 1, II:7) is a Comorian 29-year-old female. She was born from an apparently non-consanguineous marriage. Two of her sisters and 2 of her maternal aunts died in early infancy in the Comoros, without any aetiological diagnosis. The eldest sister of the index case (Fig. 1, III:1) died of unexpected sudden death at 30 months of age; autopsy was refused. The mother of the index case had viral gastroenteritis at the same time her son experienced his first episode of rhabdomyolysis. She was admitted to a medical department for dehydration. After 48 hours of treatment, moderate rhabdomyolysis was noticed (peak CK concentration 3,050 UI/L). CK quickly normalised. She had never reported muscular symptoms, such as myalgia, chronic pain, bruising, discoloration of the urine, and had no other rhabdomyolysis episode during her follow-up. She did not have a muscle biopsy.

Methods and Results

Genetic Analysis

Next-generation sequencing was performed on blood-extracted DNA from the index case with a gene panel including 30 genes involved in fatty acid oxidation defects and related disorders (gene list available upon request). The index case was found to be homozygous for the mutation c.847dupA in exon 6 of the *LPIN1* gene

(NM_001261428.1) leading to a frameshift and a premature stop codon (p.Arg283Lysfs*9). This mutation, absent from control databases, has not been previously reported. It was interpreted as a pathogenic variant as it leads to a premature stop codon upstream of the lipin-1 catalytic domain (amino acids 626–851) and probably translates into a truncated non-functional protein. The mutation was confirmed by Sanger sequencing. Unexpectedly, the mother was also found to be homozygous for this mutation (confirmed on a second sample). The healthy sister and the father were both heterozygous carriers of the mutation. No genetic analysis could be performed for the deceased sister or the mother's relatives in the Comoros.

Discussion

We report herein the first familial case of a young boy and his mother both affected by homozygous *LPIN1*-related rhabdomyolysis. Inheritance seems pseudo-dominant, due to a probably highly consanguineous family and founder effect, which have already been mentioned for Comorian populations in other diseases [Sarasin et al., 2019]. The index case experienced a first extremely severe episode of acute rhabdomyolysis at 14 months of age and a lethal second episode at 3 years of age, whereas his mother had only a moderate episode of rhabdomyolysis in adulthood. Several cases of sudden death were also reported in the family, without aetiological diagnosis.

Treatment of *LPIN1*-related rhabdomyolysis is symptomatic, based on early detection, aggressive hydration, electrolyte replacement, including bicarbonate added as necessary to avoid myoglobinuria-associated renal complications, high-energy intake from carbohydrates (with lipids contributed less than 30% of total energy), and cardiac monitoring in intensive care units. To avoid long-term complications, prevention of fever, heat, and excessive exercise as well as prompt treatment of acute illness is essential. Oral or intravenous L-carnitine (≥ 50 mg/kg/day) may also be administered during an acute presentation. New treatment possibilities are discussed based on immunosuppression/immunomodulation as lipid metabolism, and lipid signaling; inflammation may underlie the severe *LPIN1*-related rhabdomyolysis crises. Dexamethasone was shown to decrease the number of lipid droplets in lipin-1-deficient patients' myoblasts with a decrease in peak CK concentration during acute rhabdomyolysis. Recombinant IL-1 receptor antagonist and anti-IL-1 β antibody could be of potential therapeutic values [Meijer et al., 2015; Stepien et al., 2019].

To date, no paucisymptomatic patient with biallelic mutations in *LPIN1* has been reported. In a large cohort of 171 paediatric and adult patients with muscular symp-

toms, ranging from severe rhabdomyolysis (CK: >10,000 UI/L) to milder phenotypes (mild rhabdomyolysis [CK: <10,000 UI/L] or myalgia), screening of *LPIN1* found that all 18 patients who harboured 2 *LPIN1* mutations had severe episodes of rhabdomyolysis [Michot et al., 2012]. These episodes started before 6 years of age except for 2 patients (8 and 42 years), illustrating clinical interfamilial variability. No patient with biallelic mutations in *LPIN1* was diagnosed in the milder group, whereas 9 heterozygous variants in *LPIN* family genes (*LPIN1*, *LPIN2*, and *LPIN3*) were identified. In the cohort reported by Michot et al. [2012], at least 40% of heterozygous relatives had myalgia. A heterozygous symptomatic mother, presenting with myalgia, muscle weakness, general fatigue, and sleep apnoea was reported by Nunes et al [2016]. More recently, the course and outcome of a 25-year-old patient having biallelic mutations in *LPIN1* was reported after an episode of severe rhabdomyolysis (CK: 500,000 IU/L), with residual bilateral common peroneal neuropathies in addition to a background residual distal myopathy [Stepien et al., 2019]. Furthermore, Zeharia et al. [2008] described that a carrier state may predispose for statin-induced myopathy. To the best of our knowledge, the mother of the index case is the first patient to be reported as harbouring biallelic mutations in *LPIN1* and only presenting with a mild phenotype. Her case is suggestive of possible modifying factors which protect from the typical severe course of the disease. Further studies are needed in order to identify these factors and their roles. This report

expands the phenotypic spectrum of *LPIN1*-related rhabdomyolysis, illustrating high intrafamilial variability, ranging from lethal in early infancy to a paucisymptomatic form diagnosed in adulthood.

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Statement of Ethics

Patients have given their written informed consent. The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors have no conflicts of interest to declare.

Author Contributions

Linda Pons, Sonia Teyssedre, Capucine Didier, Nathalie Guffon, and Alain Fouilhoux cared for the patients. Cécile Acquaviva-Bourdain, Alice Veauville, Julie Steffann, Stéphanie Gobin, and Pascale de Lonlay performed the genetic analysis. Linda Pons wrote the first draft of the manuscript, and all other authors contributed to the manuscript final form.

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