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Case Report

LPIN1 deficiency with severe recurrent rhabdomyolysis and persistent elevation of creatine kinase levels due to chromosome 2 maternal isodisomy

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ABSTRACT

Fatty acid oxidation disorders and lipin-1 deficiency are the commonest genetic causes of rhabdomyolysis in children. We describe a lipin-1-deficient boy with recurrent, severe rhabdomyolytic episodes from the age of 4 years. Analysis of the *LPIN1* gene that encodes lipin-1 revealed a novel homozygous frameshift mutation in exon 9, c.1381delC (p.Leu461SerfsX47), and complete uniparental isodisomy of maternal chromosome 2. This mutation is predicted to cause complete lipin-1 deficiency. The patient had six rhabdomyolytic crises, with creatine kinase (CK) levels up to 300,000 U/L (normal, 30 to 200). Plasma CK remained elevated between crises. A treatment protocol was instituted, with early aggressive monitoring, hydration, electrolyte replacement and high caloric, high carbohydrate intake. The patient received dexamethasone during two crises, which was well-tolerated and in these episodes, peak CK values were lower than in preceding episodes. Studies of anti-inflammatory therapy may be indicated in lipin-1 deficiency.

1. Introduction

Acute rhabdomyolysis is a life-threatening condition. In adults it is typically due to trauma, intoxication or infection, whereas in children with recurrent rhabdomyolysis, inherited muscle disorders are frequent [1,2]. The two commonest causes of early onset recurrent, severe rhabdomyolysis in children are fatty acid oxidation disorders and mutations in the *LPIN1* gene that encodes lipin-1. Over 35 lipin-1-deficient patients are reported [3–6]. Clinically, lipin-1 deficiency is an autosomal recessive disorder presenting with episodic myalgia and myoglobinuria, most often triggered by febrile illness and less commonly by prolonged exercise, fasting and anesthesia. Myalgia can precede the increase of the creatine kinase (CK) level [7]. The rhabdomyolytic episodes of lipin-1 deficiency typically begin before 6 years of age [4,8]. Some *LPIN1* heterozygotes also experience cramps and exercise-induced myalgia [8]. Heterozygous *LPIN1* mutations have been identified in two individuals with statin-induced myopathy, suggesting that partial lipin-1 deficiency might represent a risk factor for drug-induced myotoxicity [4,9].

Over twenty *LPIN1* mutations have been described to date in several ethnic groups but no clear genotype-phenotype correlation has been shown [3–5,8]. The *LPIN1* gene spans 19 exons and a deletion mutation spanning exon 18 occurs in 86% of Caucasian families/patients [3,8]. Lipin-1 is an 890 amino acid protein [10], highly expressed in skeletal muscle, adipose tissue, liver and myocardium [11]. Lipin-1 is both an enzyme and a transcriptional regulator. Lipin-1 has phosphatidic acid phosphatase (PAP1) activity [12], converting phosphatidic acid (PA) to diacylglycerol (DAG). DAGs are substrates for the synthesis of triacylglycerols, phosphatidylcholine and phosphatidylethanolamine [13–15] and in mouse cells with severe lipin-1 deficiency, incubation with DAGs enhances autophagy and survival [16]. Lipin-1 is also a co-activator of PPARγ and PPARα, factors that control the transcription of genes of fatty acid oxidation [11,17–19]. Lipin-1 can bind NFATc4 (nuclear factor of activated T-cells) to repress inflammatory gene expression [20,21] and the relationship of rhabdomyolysis, inflammation and lipin-1 deficiency was recently reviewed [22].

We report a child with recurrent episodes of severe rhabdomyolysis, persistent elevation of creatine kinase (CK) between episodes and severe deficiency of lipin-1 caused by complete isodisomy of a

Abbreviations: aCGH, array comparative genomic hybridization; CK, creatine kinase; UPD, uniparental disomy; DAG, diacylglycerol; PA, phosphatidic acid.

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maternal chromosome 2 containing a novel homozygous frameshift *LPIN1* mutation.

2. Case report

The patient presented at 4 years of age with severe rhabdomyolysis during an upper respiratory tract infection with fever and cough, due to a metapneumovirus. His antenatal medical history was unremarkable except for maternal gestational diabetes. Psychomotor development is normal. The parents are non-consanguineous French Canadians. The mother complained of mild unexplained chronic myalgia since childhood.

There was no history of toxin ingestion or trauma. He had a 6-month history of nocturnal lower limb pain, particularly after physical exertion. Physical examination revealed unsteady gait and difficulty rising to a standing position, due to muscle pain. Laboratory evaluation showed marked elevations of creatine kinase (CK, 299,966 U/L, normal range for age, 30–200 U/L), aspartate aminotransferase (5810 U/L, normal for age, 11–43 U/L) and alanine transaminase (1050 U/L, normal for age, 11–25 U/L) but was otherwise normal. His plasma acylcarnitine profile was normal.

LPIN1 gene sequencing was performed after the second rhabdomyolytic episode, revealing homozygosity for a novel mutation in exon 9, c.1381delC (p.Leu461SerfsX47), which is predicted to produce a truncated protein lacking the functionally-essential C-LIP and PAP domains and to result in complete deficiency of lipin-1. Both parents were tested for this mutation and only the mother was found to be a carrier. Because of her history of mild chronic myalgia, physical examination and plasma CK determination were performed and were normal (CK, 90 U/L). Deletion and amplification analysis of the *LPIN1* gene was normal. To rule out non-amplification of a paternal allele (allele drop-out), exon 9 of the *LPIN1* gene was re-amplified from the father's DNA using a different set of primers, and the mutation was absent. The most likely remaining explanations were total or segmental maternal uniparental isodisomy (UPD) of chromosome 2 or non-paternity. PCR-based analysis of DNA from both parents and the patient was performed to test for UPD of chromosome 2, using 8 microsatellite markers spanning the length of chromosome 2. Seven markers were informative, and they demonstrated that the patient inherited only one set of the maternal alleles for these markers, consistent with maternal isodisomy for all of chromosome 2 (Fig. 1).

At present, the patient has had a total of 6 rhabdomyolytic episodes, three of which occurred during febrile infections. Between episodes of rhabdomyolysis, he has occasionally complained of myalgia, but his neuromuscular examination was normal. His plasma CK levels have never normalized between episodes, typically ranging between 400–700 U/L with a recorded maximum value during an asymptomatic period of 2163 U/L. For each of the rhabdomyolytic episodes, the highest recorded CK values and the duration of the episode (defined as time during which plasma CK levels exceeded 2200 U/L) were as follows: episode 1, 299,966 U/L, 6 days; episode 2, 17,450 U/L, 6 days; episode 3, 140,126 U/L, 7 days; episode 4, 11,148 U/L, 5 days; episode 5, 4434 U/L, 3 days; episode 6, 244,459 U/L, 10 days.

In each episode, high caloric intake was provided orally as high carbohydrate meals and as intravenous dextrose, with lipids contributing ≤30% of total energy intake. Intravenous fluids (10% dextrose, 0.9% sodium chloride) were initially administered at 1.5–2× maintenance rate, with other electrolytes and bicarbonate added as necessary to avoid myoglobinuria-associated renal complications. Cardiac monitoring was performed in the intensive care unit during the acute phase. L-carnitine was also given (≥50 mg/kg/day in 8 doses intravenously). The parents were provided with detailed instructions for prevention of episodes, which include exercise as tolerated, hydration during exercise and prompt consultation to the emergency department in case of myalgia or fever. In the fourth and fifth episodes, in addition to the above mentioned protocol, dexamethasone was given (0.6 mg/kg intravenously, repeated once 24 h later in episode 4 and repeated 4 times every 24 h in episode 5). Episode 6 was atypical, beginning with stridor and respiratory distress, that were treated as bronchospasm with dexamethasone (0.5 mg/kg, one dose) but also salbutamol by nebulisation (800 mcg every 20 min for 4 doses) and one dose of epinephrine (5 mg by nebulisation) following which CK increased markedly.

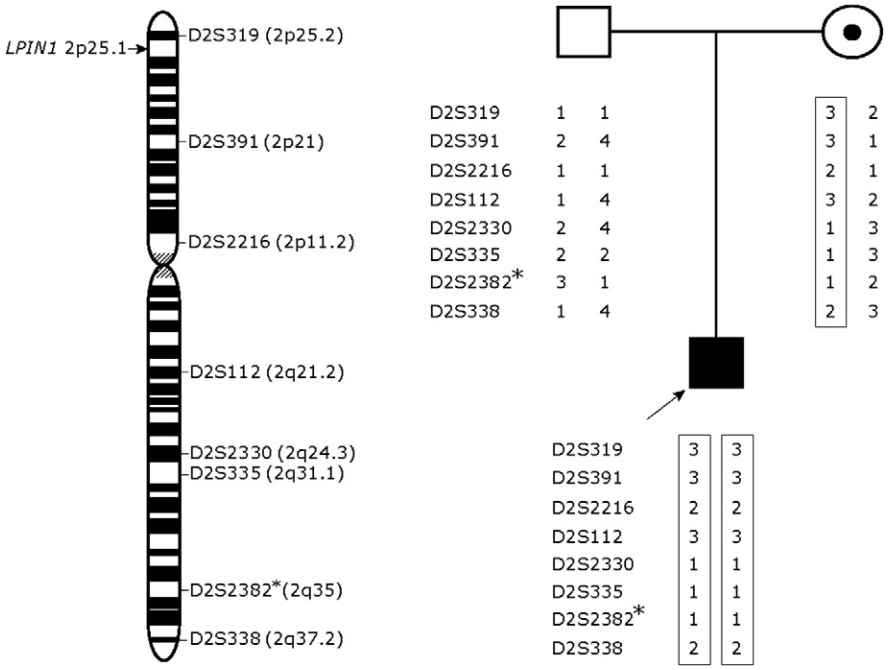

Fig. 1. UPD testing, demonstrating complete maternal isodisomy of chromosome 2 in the proband. Microsatellite markers were used to determine the parental origin of the two chromosome 2 homologs of the proband. All the informative markers (7 out of 8) were inherited from the same maternal chromosome 2. The distribution of the markers along chromosome 2 and the position of the *LPIN1* gene are depicted in the ideogram on the left of the figure. The asterisk indicates the non-informative marker.