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Case Report

A neglected cause of recurrent rhabdomyolysis, LPIN1 gene defect: a rare case from Turkey

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ABSTRACT

Background. Rhabdomyolysis; can occur due to toxic, infectious, metabolic, and genetic causes. Severe rhabdomyolysis may progress to several clinical manifestations such as cardiac arrest and may pose a risk of mortality if it is not treated timely.

Case. In this article, we presented a 26-month-old patient who was admitted with an acute rhabdomyolysis attack and a venovenous hemodiafiltration (CVVHDF) was initiated on the 5th hour of hospitalization. Creatine kinase (CK) levels of the patient continued to increase (max: 943 452 IU/L) until the 5th day of treatment and hereafter began to decrease. As the common causes of rhabdomyolysis were excluded and the CK levels were the highest values reported in the literature, although, LPIN1 deficiency was the most suspected diagnosis, to facilitate the diagnostic procedures a whole-exome sequencing was performed. A homozygous [c.1696G>C p. (Asp566His)] mutation was detected on LPIN1 gene. This variant has not been described previously, however, when examined with programs such as SIFT and Mutation taster, it has been considered as pathogenic.

Conclusion. In the pediatric age group, especially in infants presenting with severe rhabdomyolysis, LPIN1 deficiency should also be considered; as early diagnosis and appropriate treatment may reduce mortality.

Key words: creatine kinase, rhabdomyolysis, LPIN1 deficiency.

Rhabdomyolysis can occur both due to metabolic and genetic diseases and also acquired causes like trauma, exercise, drugs, and toxins. Severe rhabdomyolysis may progress to several clinical manifestations such as cardiac arrest and may pose a risk of mortality if it is not treated timely.1

Most of the metabolic myopathies characterized by recurrent myoglobinuria triggered by fever and exercise are composed of glycogen storage diseases, fatty acid oxidation defects, carnitine metabolism disorders, and myopathic mitochondrial cytopathies. All of those reasons cause an energy shortage in the muscles. Differential diagnosis is very important in distinguishing metabolic myopathies. Particularly, muscle myophosphorylase activity and glycogen accumulation may provide specific diagnostic information for muscle glycogenosis. Additionally, staining and quantitative enzymatic analyzes for oxidative phosphorylation chain complexes may provide insight into single or combined oxidative phosphorylation chain deficiencies. However, the diagnosis of muscle biopsy in this highly genetic heterogeneous group is very limited. In pediatric patients presenting with rhabdomyolysis, when a specific diagnosis could not be made by first step metabolic analyses, electromyography, muscle biopsy (after the acute phase), and mitochondrial DNA

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analysis may be performed. Despite all these investigations, the cause of rhabdomyolysis may not be found in at least half of the cases. Mutations of the \textit{LPIN1} gene have been identified as the cause of severe recurrent rhabdomyolysis in pediatric patients. \textit{LPIN1} gene defects have an autosomal recessive hereditary model. Biallelic mutations cause severe, recurrent rhabdomyolysis attacks with high-mortality rates, although there are only a few cases reported in the literature when compared to other metabolic myopathies. The pathophysiology of Lipin 1 deficiency is not well known and the prognosis is poor.\textsuperscript{2,3} Lipin 1 is found most abundant in the adipocytes and skeletal muscle, and it acts as a transcriptional coactivator by interacting with transcription factors that regulate the expression of genes involved in energy pathways.\textsuperscript{4,5} It is thought that rhabdomyolysis which develops in \textit{LPIN1} deficiency may be caused by disruptions in all these functions, but further studies are needed to clarify the pathogenesis.

In this article, we describe a patient with acute rhabdomyolysis, who to the best of our knowledge had the highest creatine kinase (CK) level reported in the literature. She was diagnosed with \textit{LPIN1} deficiency, with a homozygous missense mutation which was not previously described in the literature. With an effective and immediate intensive care treatment and CVVHDF, we successfully got over this severe rhabdomyolysis attack.

**Case Report**

A twenty-six months old girl admitted to the emergency department with complaints of loss of appetite for 2-3 days and somnolence on the last day. She also had a fever. Dark color of the urine was first observed in the emergency department (Fig. 1) before high levels of serum CK: 10 529 IU/L (reference range: 29-168), AST (aspartate aminotransferase): 229 IU/L (reference range: 5-40), and ALT (alanine aminotransferase): 53 IU/L (reference range: 7-40) were determined. CK level was increased to 40 850 IU/L at the 4\textsuperscript{th} hour of admission. The patient was transferred to the pediatric intensive care unit with the diagnosis of rhabdomyolysis, when a rapid rise in muscle enzymes together with a change of consciousness was observed. However, her renal function and blood gas analysis were normal.

Prenatal and natal history was unremarkable. The patient did not have similar symptoms before and her neuromotor development was appropriate for the age. Her parents were first degree cousins, she had a healthy sister and there was no family history of rhabdomyolysis. On physical examination, the Glasgow Coma Score was 8, blood pressure was 98/58 (65) mmHg, and heart rate was 160/min. There was no pseudohypertrophy and muscle weakness. Systemic examination was normal except for the change in consciousness, nystagmus and dark color of the urine. Laboratory evaluation revealed; BUN: 20 mg/dl, creatinine: 0.6 mg/dl, uric acid: 6.5 mg/dl, Na: 138 mmol/L, K: 3.8 mmol/L. Electrocardiogram (ECG) and echocardiography which were performed to exclude cardiac pathologies and rhythm disorders put forward normal results. Urine ketone was positive. Toxic causes were excluded by a detailed history and with toxicological studies. Blood and urine culture tests and

**Fig. 1.** Change in the urine color of the patient within 4 hours.
viral serology for infectious agents were also negative.

For initial treatment; 3000 ccs/m² intravenous fluid, urine alkalization, and diuretic were given. Since the patient’s consciousness was gradually worsened, she was intubated. Serum (reference range: 0-65), and urine myoglobin levels (normal<5 ng/ml) were measured over than 5000 ng/ml. CK was 170 000 IU/L at the 5th hour of admission, and continuous venovenous haemodiafiltration (CVVHDF) was started. Creatine kinase values continued to increase in the first 4 days of hemodiafiltration (The peak CK: 943 452 IU/L, AST: 9599 IU/L, ALT: 2616 IU/L; at the 5th day of CVVHDF), and then they began to decrease. Hemodiafiltration was discontinued on the 9th day of hospitalization, following a reduction of CK level to 26 467 IU/L (Fig. 2). On the 12th day of hospitalization, she was extubated. Serum glucose, ammonia, lactate, carnitine-acyl carnitine profile, homocysteine, plasma amino acids, and urine organic acid analysis, which were taken in the critical period were normal. The blood ketone level was within the normal limits. In this step differential diagnosis is very important, although the LPIN1 gene defect was considered in the foreground. As inherited causes of rhabdomyolysis are a large group of diseases, it is time-consuming to evaluate all of them. So whole-exome sequencing was performed and a homozygous [c.1696G>C p. (Asp566His)] mutation of the LPIN1 gene was detected. This variant has not been described previously, but when evaluated with programs such as SIFT and Mutation taster, it has been considered as pathogenic. Mother, father, and sister are tested with Sanger’s sequencing. The mother, father, and sister were heterozygous for this mutation (Fig. 3). Eleven months after the first attack of rhabdomyolysis, the patient is still healthy.

We gave information and took informed consent from the parents of the patient.

Discussion

Metabolic myopathies characterized by recurrent myoglobinuria and triggered by catabolic processes like fever and exercise are glycogen storage diseases, fatty acid oxidation defects, carnitine metabolism disorders, and mitochondrial pathologies. Differential diagnosis is very important in distinguishing metabolic myopathies which are a crowded group from the other acquired conditions or neurological causes. Basic metabolic examinations are guiding in the first stage of diagnosis, especially in fatty acid oxidation.

![Fig. 2. Change of creatine kinase (CK) values of the patient in course of time (h: hour, d: day).](image-url)

- ▼: Hemodiafiltration initiation time
- ❖: Hemodiafiltration termination time
defects, if critical samples were taken in time. Since our patient’s plasma ammonia level was normal, urine ketone was positive and blood ketone was normal; fatty acid oxidation defects were excluded. Due to the normal detection of carnitine levels and the acylcarnitine profile, another frequent cause of CPTII deficiency was also excluded. Some of the mitochondrial myopathies that have an important role in the differential diagnosis are characterized with neuromotor retardation and myopathic findings. However, our patient did not have any neurological abnormalities and plasma lactate/pyruvate levels were normal. Then after, with very high CK levels LPIN1 gene defect was our preliminary diagnosis. Muscle biopsy is an option if any abnormal finding is detected in the first step of metabolic examinations. However, the diagnostic value of muscle biopsy in this highly heterogeneous genetic disease group is limited and can be done 1 or 2 months after the acute phase. Molecular tests are increasingly being used to explore the genetic cause of rhabdomyolysis. Like our case, in severe rhabdomyolysis without a known neurological disease and normal metabolic investigation results which are ruling out fatty oxidation defects, mitochondrial pathologies, and glycogen storage diseases, the diagnosis is based on molecular analysis.

LPIN1 gene defect is a common cause of childhood serious rhabdomyolysis, which accounts for more than half of the cases in infancy. The first attack of rhabdomyolysis usually occurs during a febrile illness like in our case. The lipin 1 protein plays a critical role in adipocyte differentiation and lipid metabolism. However, further studies are needed to determine which changes in these pathways bring out the symptoms.

Acute renal failure and cardiac arrhythmia are the most critical complications of rhabdomyolysis and are usually associated with high mortality if the patients have not renal replacement therapy in time. In our case, no abnormal ECG findings were observed. In one case reported by Bergounioux et al., ECG had shown diffuse symmetrical high-amplitude T waves with no other changes. No specific ECG findings have been reported in other articles. Although there is not a specific treatment, early suspicion of LPIN1 deficiency will lead to a better prognosis and avoid unnecessary invasive procedures such as muscle biopsy. Michot et al.; reported that from 29 infantile cases with rhabdomyolysis, whose etiology could not be determined and all metabolic myopathies were excluded, 59% of them had LPIN1 gene mutations. Our case also had a homozygous missense mutation on the LPIN1 gene, which was not described.

In this article; we present an infantile case of severe rhabdomyolysis, which was triggered by a febrile illness, to share a rare disease of LPIN1 deficiency. Also, to the best of our knowledge, this case has the highest CK levels reported in the literature with LPIN1 deficiency and also the first case with LPIN1 deficiency described from Turkey.
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