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Recurrent Rhabdomyolysis after Kidney Transplant in Adult-Onset VLCAD Deficiency

Erişkin Başlangıçlı VLCAD Eksikliğinde Böbrek Nakli Sonrası Tekrarlayan Rabdomiyoliz

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Abstract

Very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency is a hereditary disorder of mitochondrial long-chain fatty acid oxidation. It is a syndrome characterized by rhabdomyolysis, muscle necrosis, and release of intracellular muscle components into the circulation. A 29-year-old male patient with hypertension, arrhythmia, and preemptive renal transplantation history was admitted to our clinic with complaints of recurrent hematuria attacks, body pain, and dizziness. No erythrocytes were observed in the microscopic field of urine sediment. In genetic analysis, a homozygous mutation was detected in the ACADVL gene in the NM_000018.4 C.1500_1502del CCT p. L502del variation, and VLCAD deficiency was diagnosed. We planned to discuss the case with the literature in order to emphasize that metabolic myopathies should also be evaluated in the etiology of patients who develop acute renal failure presenting with recurrent non-traumatic exercise-associated rhabdomyolysis.

Keywords: Rhabdomyolysis, Very Long-Chain Acyl-CoA Dehydrogenase, Kidney Transplant

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Öz

Çok uzun zincirli asil-CoA dehidrogenaz (VLCAD) eksikliği, mitokondriyal uzun zincirli yağ asidi oksidasyonunun kalıtsal bir bozukluğudur. Rabdomiyoliz, kas nekrozu ve hücre içi kas bileşenlerinin dolaşıma salınmasıyla karakterize bir sendromdur. Hipertansiyon, aritmi ve preemptif böbrek nakli öyküsü olan 29 yaşında erkek hasta, tekrarlayan hematüri atakları, vücut ağrısı ve baş dönmesi şikayetler ile kliniğimize başvurdu. İdrar sedimentinin mikroskobik alanında eritrosit izlenmedi. Genetik analizde NM_000018.4 C.1500_1502del CCT p. L502del varyasyonunda ACADVL geninde homozigot mutasyon tespit edildi ve VLCAD eksikliği tanısı konuldu. Tekrarlayan travmatik olmayan egzersiz ilişkili rabdomiyolizle başvuran akut böbrek yetmezliği hastalarının etyolojisinde metabolik miyopatilerin de değerlendirilmesi gerektiğini vurgulamak amacıyla olguyu literatür eşliğinde tartışmayı planladık.

Anahtar Kelimeler: Rabdomiyoliz, Çok Uzun Zincirli Açil-CoA Dehidrogenaz, Böbrek Nakli

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Introduction

Very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency is a hereditary disorder of mitochondrial long-chain fatty acid oxidation. The prevalence, as detected by newborn screening, is reported to be 1 in 42,500 (1). The clinical spectrum ranges from severe cardiomyopathy and death within the first few days of life to recurrent hypoketotic hypoglycemia, and in adult-onset forms, may manifest as myopathy and/or rhabdomyolysis.

Rhabdomyolysis is a syndrome characterized by muscle necrosis and the release of intracellular muscle components into the circulation (2). It leads to acute kidney injury due to tubular obstruction caused by pigment, proximal tubular epithelial cell damage, and reduced blood flow resulting from vasoconstriction in the outer medulla (2).

In this report, we present a rare case of VLCAD deficiency diagnosed in an adult patient who developed recurrent rhabdomyolysis attacks after preemptive kidney transplantation while being followed for chronic kidney disease of unknown etiology.

Case Presentation

A 29-year-old male patient with a history of hypertension, arrhythmia, and preemptive kidney transplantation (donor: mother, 7 years ago) presented to our clinic with complaints of recurrent hematuria, body aches, and dizziness. The laboratory results at the time of admission are shown in Table 1. His medical history revealed that the cause of his primary kidney failure was unknown, and he had not undergone a kidney biopsy. There was a history of consanguinity between his parents, and his sister had proteinuria. After discharge post-transplant, his serum creatinine was 1.4 mg/dL, and he had received treatment for cytomegalovirus (CMV) colitis. Four years prior, he had undergone coronary angiography due to chest pain, which revealed normal coronary arteries. The patient had also presented earlier with cola-colored urine and developed a need for hemodialysis, although microscopic analysis of his urine sediment did not show any erythrocytes at that time.

Table 1.
Laboratory Results at The Time of Admission

Parameter (Reference intervals)	Result
Creatinine (0.67-1.17)	2.45 mg/dL
Potassium (3.5-5.1)	5.9 mmol/L
eGFR (estimated glomerular filtration rate)	35 mL/min
Phosphorus (2.8-4.5)	5.64 mg/dL
Albumin (35-52)	48.4 g/L
Uric acid (2.6-7.2)	7.8 mg/dL
BUN (Blood Urea Nitrogen) (6-20)	36 mg/dL
HCO3 (Standard Bicarbonate) (22-26)	22.5 mmol/L
Creatine Kinase (CK) (20-200)	84,424 U/L
Cyclosporine 0-hour drug level	89.11 µg/L
Myoglobin (28-72)	19,457 µg/L
Hemoglobin (12.8-16.7)	15.4 g/dL
PTH (Parathyroid Hormone) (12-88)	240 pg/mL
ALT (Alanine Aminotransferase) (0-45)	894 U/L
AST (Aspartate Aminotransferase) (0-35)	213 U/L
Alkaline Phosphatase (30-120)	45 U/L
GGT (Gamma-Glutamyl Transferase) (0-55)	21 U/L
Total Bilirubin (0.3-1.2)	0.47 mg/dL
LDH (Lactate Dehydrogenase) (<248)	2,735 U/L
CRP (C-Reactive Protein) (<5)	77.3 mg/L
TSH (Thyroid Stimulating Hormone) (0.27-4.2)	3.45 mIU/L
Free T4 (Thyroxine) (0.93-1.7)	1.23 ng/dL
Free T3 (Triiodothyronine) (2-4.4)	2.42 ng/dL
Urine pH (5-7.5)	6
Urine Protein (<15)	>=300 mg/dL
Urine Erythrocytes	>=200

On examination, under immunosuppressive therapy (Cyclosporine, prednisolone and Mycophenolate mofetil) his body temperature was 36°C, heart rate 104 beats per minute, respiratory rate 18 breaths per minute, and blood pressure 140/70 mmHg. His transplanted kidney was palpated normally in the right lower quadrant. Neurological examination showed no muscle weakness. Abdominal imaging revealed atrophic native kidneys, but no masses were identified. The transplanted kidney appeared normal on ultrasound in terms of size, parenchymal thickness, and echogenicity. Echocardiography showed an ejection fraction of 65%, with left ventricular hypertrophy. His creatine kinase (CK) and myoglobin levels were elevated. Electromyography revealed mixed short-duration, low-amplitude, polyphasic myogenic motor unit action potentials (MUAPs) in the right deltoid and rectus femoris muscles, with normal findings in other muscle groups. There was no abnormal spontaneous activity in the examined extremity muscles.

The patient did not have any history of trauma, electrolyte imbalance, hypothyroidism, statin use, exposure to toxic substances, or anesthetic agents. Infectious screening did not reveal any pathology, and his immune panel was negative. Given his history of muscle pain and recurrent hematuria after prolonged fasting, with elevated CK and myoglobin levels and no erythrocytes seen in the urine sediment, genetic testing revealed a homozygous mutation (NM_000018.4 C.1500_1502del CCT p. L502del) in the ACADVL gene, confirming the diagnosis of VLCAD deficiency. The patient was referred to a specialized neurology center for further management of metabolic and muscle diseases.

Discussion

The classic triad of rhabdomyolysis includes myalgia, muscle weakness, and cola-colored urine; however, this triad is observed in less than 10% of cases. The etiology of rhabdomyolysis can be classified into three main categories: trauma and compression (e.g., crush syndrome), non-traumatic exercise-related (e.g., metabolic myopathies in less than 10% of cases), and non-traumatic, non-exercise-related (e.g., medications, toxins, infections) (3,4).

VLCAD deficiency, which occurs in the mitochondrial inner membrane, catalyzes the initial step of long-chain fatty acid β-oxidation. This mitochondrial enzyme is crucial for energy production in the mitochondria via fatty acid oxidation. VLCAD deficiency is inherited in an autosomal recessive pattern and can present with three clinical forms: a severe early-onset form with cardiomyopathy and high mortality; an intermediate form starting in childhood with hypoketotic hypoglycemia and a better prognosis; and an adult-onset form characterized by isolated skeletal muscle involvement, rhabdomyolysis, and myoglobinuria triggered by exercise or fasting. It is the second most commonly diagnosed disorder in fatty acid oxidation (1,5).

In patients with severe childhood-onset VLCAD deficiency, mutations typically lead to complete loss of enzyme activity, resulting in cardiomyopathy and early mortality. In contrast, adult-onset or milder childhood-onset phenotypes often carry mutations that allow for residual enzyme activity(6), which may protect against early severe manifestations but predispose to exercise- or fasting-induced rhabdomyolysis. In this case, the p.L502del variant is likely associated with residual enzyme activity, consistent with the patient's adult-onset myopathic presentation.

In our case, there was no history of trauma, crush syndrome, prolonged immobilization, burns, electrical injury, or other direct muscle damage, and the patient had no known history of alcohol use, carbon monoxide exposure, or drug use that could lead to rhabdomyolysis. Laboratory analyses revealed no electrolyte imbalance, and thyroid function tests were normal. There were no signs of active infection.

No laboratory data from before the kidney transplantation were available, as the cause of end-stage renal disease had not been determined. It is possible that the underlying VLCAD deficiency contributed to renal dysfunction prior to transplantation. Furthermore, the use of immunosuppressive medications, particularly corticosteroids, during the peri-transplant period may increase metabolic stress and trigger episodes of rhabdomyolysis, potentially revealing previously silent disease.

The absence of a myogenic response in the left deltoid muscle was intentional, as this muscle was preserved for a potential biopsy. Therefore, no abnormal spontaneous activity was recorded in that region during electromyography.

In patients presenting with recurrent, non-traumatic, exercise-related rhabdomyolysis and acute kidney failure, metabolic myopathies should be considered in less than 10% of cases (3,7). Genetic and metabolic evaluations are essential, particularly in patients with a history of muscle pain, myoglobinuria, and acute kidney injury triggered by fasting, infections, or physical exertion.

The differential diagnosis of recurrent, non-traumatic rhabdomyolysis is broad. Glycogen storage diseases, particularly McArdle disease, may present with exercise intolerance and myoglobinuria. Channelopathies and myotonias can also produce episodic muscle breakdown. Additionally, drug- or toxin-induced myopathies, endocrine disturbances (including hypothyroidism and adrenal insufficiency), electrolyte imbalances, and certain infections must be excluded (8,9).

Patients should avoid prolonged fasting, strenuous exercise, and other catabolic stressors. Nutritional strategies include frequent carbohydrate-rich meals, restriction of long-chain fatty acids, and supplementation with medium-chain triglycerides (MCTs). In selected patients, triheptanoin therapy may reduce the frequency of rhabdomyolysis episodes (10). During acute attacks, aggressive hydration, urine alkalinization, and renal replacement therapy if needed are recommended. Long-term follow-up should be multidisciplinary, involving nephrology, neurology, and metabolic specialists.

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