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Acute Rhabdomyolysis Due To Levetiracetam in A Two-Year-Old Girl

İki Yaşındaki Kız Çocuğunda Levetirasetama Bağlı Akut Rabdomiyoliz

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ABSTRACT

Levetiracetam is one of the safest drugs which is used for the treatment of focal and generalized seizures during childhood. Until now, few patients have been reported with the diagnosis of acute rhabdomyolysis due to levetiracetam and our case is the youngest patient in the literature. Two-year old girl followed with atypical Rett syndrome (CDKL 5 deficiency) was admitted to our hospital with pneumonia and respiratory insufficiency. She was receiving intravenous antibiotics and levetiracetam therapy. During follow-up, the increase of creatine kinase levels continued, intravenous hydration and alkalinization was added on therapy. As we could not find any etiology explaining the raising creatine kinase levels in our patient, levetiracetam was thought to be the cause of rhabdomyolysis and withdrawn. After discontinuation of levetiracetam, creatine kinase levels began to decline within 24 h and returned to normal levels in one week.

Levetiracetam-induced rhabdomyolysis is quite rare but is a life-threatening condition and should be kept in mind especially during childhood. The creatine kinase levels and renal function tests of all patients should be followed in the first week of levetiracetam therapy. Early diagnosis and supportive therapy is very important in order to prevent acute kidney injury. CDKL 5 deficiency can be a protective factor which might prevent acute kidney injury in our patient but more research is needed about this topic.

Key Words: , CDKL5, Levetiracetam, rhabdomyolysis

ÖZ

Levetirasetam çocukluk çağında fokal ve jeneralize nöbetlerin tedavisi için kullanılan en güvenilir antiepileptik ilaçlardan birisidir. Şimdiye kadar levetirasetama bağlı akut rabdomiyoliz tanılı az sayıda hasta bildirilmiştir ve vakamız literatürde bildirilmiş en genç vakadır. Atipik Rett sendromu (CDKL5 eksikliği) tanısıyla izlenen iki yaşındaki kız hasta pnömoni ve solunum yetmezliği nedeniyle hastanemize kabul edildi. İntravenöz antibiyotik ve levetirasetam tedavisi alıyordu. Klinik izleminde kreatin kinaz düzeylerinde yükselme devam etti, intravenöz hidrasyon ve alkalinizasyon tedavisine eklendi. Kreatin kinaz düzeylerinde yükselmeyi açıklayacak neden bulamadığımız için hastamızda rabdomiyolizin levetirasetama bağlı olabileceği düşünüldü ve levetirasetam tedavisi kesildi. Levetirasetam kesildikten sonra 24 saat içerisinde kreatin kinaz düzeyi düşmeye başladı ve bir hafta içersinde normal düzeylerine döndü.

Levetirasetama bağlı rabdomiyoliz çok nadir fakat hayatı tehdit eden bir durum olup özellikle çocukluk çağındaki hastalarda akılda tutulmalıdır. Levetirasetam tedavisinin ilk haftasındaki tüm hastaların kreatin kinaz düzeyleri ve böbrek fonksiyon testleri izlenmelidir. Erken tanı ve tedavi akut böbrek hasarını önlemek açısından çok önemlidir. CDKL5 eksikliği hastamızda akut böbrek hasarını önleyecek koruyucu faktör olabilir ancak bu konuyla ilgili daha fazla sayıda araştırmaya ihtiyaç vardır.

Anahtar Kelimeler: Çocuk, CDKL5, Levetirasetam, rabdomiyoliz

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INTRODUCTION

Levetiracetam (LEV) is a second-generation anti-epileptic which regulates the synaptic neurotransmitters by binding to synaptic vesicle protein 2A. Its side effects mainly include somnolence, headache, fatigue, dizziness, vomiting, and behavioral alterations. Rhabdomyolysis as a rare adverse effect of LEV was reported firstly from Japan in the literature in 2014 (1,2).

Rhabdomyolysis results from the rapid breakdown of skeletal muscle fibers which leads to leakage of potentially toxic cellular content into the systemic circulation. Although consensus criteria are lacking, the most-used definition of rhabdomyolysis is a serum creatine kinase level greater than 5 times the upper limit of normal or greater than 1000 U/L. Some of the common causes of rhabdomyolysis include trauma, strenuous exercise, seizures, hypothermia, malignant hyperthermia, electrolyte imbalances (hypokalemia, hypocalcemia, hypophosphatemia), myositis, inherited metabolic diseases such as dystrophies/myopathies, glycogenolysis/glycolysis metabolism disorder, mitochondrial disorders, and certain drugs (statins and succinylcholine). Febrile illnesses and exercise are common triggers of rhabdomyolysis (3).

Rhabdomyolysis may be due to a combination of underlying genetic disorder and environmental triggers. Genetic disorders underlying rhabdomyolysis cause a diagnostic challenge due to their rarity, marked heterogeneity, and nonspecific clinical features requiring a high index of suspicion. Acquired causes are frequently observed. The underlying pathophysiology of this adverse effect is unknown. The increase of intracellular calcium concentration by direct injury to sarcolemma (acquired causes) or the failure of energy production (inherited causes) leading to Na/K-ATPase and Ca2+ATPase pumps dysfunction and skeletal muscle fiber necrosis are pathopysiologic mechanisms causing rhabdomyolysis (4).

We report 2-year-old girl who developed rhabdomyolysis 24 hours after the initiation of LEV, and improved rapidly after withdrawal of this drug.

CASE REPORT

Two-year old girl was admitted to our clinics with pneumonia and respiratory insufficiency. She has been followed with the diagnosis of atypical Rett syndrome (CDKL deficiency) at a different center. She was receiving no antiepileptic drugs and investigated for all inherited metabolic diseases.

She was hospitalized for pneumonia at a different center. She was born after an uncomplicated full-term pregnancy. She had generalized tonic-clonic seizures lasting 20-30 seconds since two months. Phenobarbital, klonazepam, vigabatrin and ACTH were given but seizures did not respond to these drugs. After the diagnosis of CDKL5 deficiency, all antiepileptic drugs were withdrawn because atypical Rett syndrome was thought to be refractory to all antiepileptics. During clinical follow-up, she had seizure lasting for 4-5 minutes and levetiracetam was given with loading dose to treat seizure and antimicrobial therapy (ceftriaxone) for pneumonia. Due to clinical and laboratory (increase in CK,AST,ALT levels) deterioration, she was transferred to our hospital. At our hospital, LEV was continued, cefotaxim and vancomycin were given. Thorax ultrasonography showed bilateral pleural effusion so diagnostic tab was performed and chest tube was inserted by pediatric surgeons. The patient improved remarkably after pleural drainage and control ultrasonography revealed bilateral minimal pleural effusion. During the follow-up, raising CK levels were observed, Intravenous (IV) hydration (1/3 SF) and alkalinization (4 meq/kg NaHCO3,after two days decreased to 2 meq/kg) was added on therapy. After IV hydration and bicarbonate, CK levels continued to rise and reached a level of 71280 U/L (N:33-211). Laboratory investigations revealed high levels of liver function tests (AST:1502 U/L, N:0-46; ALT: 410 U/L, N:8-32). We could not measure serum or urine myoglobin levels. We did not observe dark urine. There was no history of prolonged convulsion. Viral serology was negative. The result of all the metabolic tests were normal. We could not find out any explanation for this unexpected and resistant increase in CK level, for this reason LEV was thought to be the cause of acute rhabdomyolysis and withdrawn. After discontinuation of LEV, CK and liver function tests began to decrease. (CK, AST, ALT levels respectively 32000,949,511; 9211,281,309; 1752,107,166; 731,68,110; 298,59,49). The laboratory tests returned to normal levels at the end of ten days and she was discharged. We diagnosed the patient as rhabdomyolysis induced by LEV based on the clinical course.

DISCUSSION

We present the youngest patient with rhabdomyolysis due to LEV in the literature. Though causality can't be completely established, on the basis of the previously reported side effect of LEV and temporal relationship between clinical and laboratory improvement after discontinuation of this drug, it was likely LEV that caused the rhabdomyolysis in our patient. Fever and serious infection were also important triggers which caused severe acute myolysis with a CK level > 50.000U/L.

Up to date, fourteen patients with LEV-induced rhabdomyolysis were reported and most of them were observed in young and adolescent patients in the literature (5-10). In a recent review analyzing 13 patients, all the patients had elevation in CK level

within 12–36 h after initiation of LEV, supporting the importance of close follow-up, particularly during the initial treatment phase (11). The time duration from initiation of LEV to peak CK elevation was 3–5 days. After the medication was discontinued, improvement in CK levels was observed in all patients. Peak CK levels observed in these cases ranged between 1368 IU/L - 49 539 IU. Our patient is the youngest case with the highest CK level (71280 IU/L) in the literature. Some reports support the idea that there is a relationship between muscle mass and peak CK levels, but our case is inconsistent with this idea.

The myoglobin level rises before CK level, can be measured in serum or urine to confirm the diagnosis but has some limitations and disadvantages. Because it has a half-life of only 1-3 hours and causes a high false-negative rate. Unfortunately, serum or urine myoglobin could not be measured in our patient. The goal of of the treatment for rhabdomyolysis is to preserve renal functions and prevent acute kidney injury (AKI). There is consensus that this can be achieved by administration of IV fluids. There is no set guideline for adult or pediatric patients but normal saline is the most commonly used fluid choice. Animal studies have shown that alkalinization of urine decreases cast formation in the acute management of rhabdomyolysis (12). Early hydration and alkalinization therapy might be a protective factor which prevented the development of AKI in our case. Mortality rate is higher especially in the patients with acute renal failure. Fortunately, renal functions were normal and there was no need for renal replacement therapy in our case.

The present case was diagnosed with atypical Rett syndrome at a different center. CDKL5 deficiency disorder (CDD) is a complex of clinical symptoms resulting from the presence of non-functional CDKL5 protein, i.e., serine-threonine kinase (previously referred to as STK9), or its complete absence. The clinical picture is characterized by epileptic seizures which initiates within the first three months of life and mostly do not respond to pharmacological treatment, epileptic encephalopathy secondary to seizures, and retardation of psychomotor development, which are often observed in the first months of life (13). An interesting study investigating the relationship between CDKL5 and rhabdomyolysis by Kim et al. (14) identified cyclin-dependent kinase-like 5 (Cdkl5), as a critical regulator of renal tubular epithelial cell (RTEC) dysfunction associated with nephrotoxic and ischemia-associated AKI. In this study, the researchers examined the role of Cdkl5 in rhabdomyolysis-associated AKI and found the activation of Cdkl5 in RTECs early during the development of rhabdomyolysis-associated AKI by using activation-specific antibodies and kinase assays. RTEC dysfunction and cell death are among the key pathological features of AKI. Diverse stress conditions such as sepsis, rhabdomyolysis, nephrotoxic drugs can trigger RTEC dysfunction. On the basis of this knowledge, we can propose that CDKL5 deficiency might be a protective factor which prevented rhabdomyolysis-associated renal impairment in our patient but more research is needed about this topic.

Lipin-1 deficiency has been reported as the second most common cause of early-onset rhabdomyolysis after primary fatty acid oxidation disorders. Phosphatidate phosphatase-1 (lipin-1) is encoded by LPIN1gene. LPIN1-related rhabdomyolysis occurs usually in children less than 6 years. Lipin-1 is highly expressed in myocardium and involved in fatty acid metabolism in the cardiomyocytes. After exclusion of primary fatty acid oxidation disorders, lipin-1 deficiency should be suspected in the presence of recurrent rhabdomyolysis, positive family history, exercise intolerance or recurrent muscle cramps (15). We planned to investigate lipin-1 deficiency if recurrent rhabdomyolysis occurs in our patient.

In conclusion, LEV-induced rhabdomyolysis is quite rare but is a life-threatening condition and should be kept in mind especially during childhood. To our current knowledge, this is one of the few reports of rhabdomyolysis due to LEV therapy in children. Early diagnosis and supportive therapy is very important. The CK levels and renal function tests of all patients should be followed in the first week of therapy. Although our patient had risk factors such as young age, serious infection treated with nephrotoxic agent (vancomycin), very high CK levels, she did not develop AKI. CDKL 5 deficiency can be a protective factor which might prevent AKI in our patient, but more research is needed about this topic.

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