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Entecavir Induced Severe Myopathy: An Uncommon Side Effect

Entekavir ile İndüklenen Şiddetli Miyopati: Nadir Bir Yan Etki

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Abstract

Chronic Hepatitis B virus (HBV) infection is a chronic viral illness that affects millions of people around the world and can cause serious consequences such as hepatic failure and hepatocellular carcinoma. Entecavir, a guanosine nucleoside analog (NA), is a commonly used and generally safe therapeutic agent in HBV infection. In this paper, we aimed to present a case of chronic HBV that developed severe myopathy as an extremely rare side effect after the use of entecavir. Patients receiving entecavir therapy for chronic HBV should be closely monitored for the development of myopathy as well as other known and common side effects.

Keywords: Hepatitis B, Antiviral therapy, Nucleoside analog.

Özet

Kronik Hepatit B virusu (HBV) enfeksiyonu, dünya çapında milyonlarca insanı etkileyen ve karaciğer yetmezliği ve hepatoselüler karsinoma gibi ciddi sonuçlara neden olabilen kronik viral bir hastalıktır. Bir guanozin nükleozit analoğu (NA) olan entekavir, HBV enfeksiyonunda yaygın olarak kullanılan ve genellikle güvenli bir terapötik ajandır. Bu yazıda, entekavir kullanımından sonra son derece nadir bir yan etki olarak şiddetli miyopati gelişen bir kronik HBV olgusunu sunmayı amaçladık. Kronik HBV için entekavir tedavisi alan hastalar, miyopati gelişimi ve diğer bilinen ve yaygın yan etkiler açısından yakından izlenmelidir.

Anahtar Kelimeler: Hepatit B, Antiviral tedavi, Nükleozit analoğu.

Introduction

Chronic Hepatitis B virus (HBV) infection influences millions of individuals globally and can cause serious comorbidities such as cirrhosis, liver failure and hepatic malignities over time [1,2]. Nucleoside analogs (NA's) and interferons are therapeutic agents used for chronic HBV infection. The mechanism of action of NA's is based on inhibiting viral polymerase activity [3,4]. Administration of NA in the management of chronic HBV, the risk of development of HBV-related complications has been significantly reduced. Entecavir is a guanosine nucleoside analog used for this purpose [1,3]. It is a globally used and safe agent in the management of HBV, but this drug has some side effects. Usually seen side effects are nausea, headache, malaise, and flu like symptoms. All these side effects are usually mild to moderate [4]. However, entecavir-associated severe myopathy is an extremely rare

side effect [4]. In this paper, we aimed to present a patient with severe myopathy due to entecavir use.

Case Report

A 50-year-old male patient who was followed up for chronic HBV was admitted to the gastroenterology outpatient clinic with complaints of muscle pain in both lower extremities and muscle weakness. He stated that myalgia and progressive weakness in the lower extremities had started 2 months ago and he did not have these complaints before. The patient had difficulty to climbing the stairs and he was complaining about getting up from a sitting position. However, there was no weakness in the upper extremities, and did not describe dysphagia or dyspnea. The patient had a known history of chronic HBV infection for 3 years and had been using entecavir tablet therapy at a dose of 0.5 mg/day for HBV infection for the last 1 year. Since the first diagnosis of chronic HBV infection, the patient declared that telbivudine treatment was used for the first two years and that the entecavir tablet therapy was used for the last year. He was not currently using any other medication other than entecavir therapy. He denied ever using alcohol, smoking and other herbal or folk remedies. His family history was negative for muscle disorders. The general condition of the patient was good, conscious, and cooperative. He stated that his physical activities were not intense. Physical examination revealed no abnormal findings other than splenomegaly that slightly crosses the rib border. In laboratory tests, serum aspartate aminotransferase and alanine aminotransferase levels were 96 IU/L and 74 IU/L, respectively. Serum direct bilirubin level was within normal range and total bilirubin level was 1.5 mg/dL. The patient's serum creatine kinase level was 1242 IU/L on admission. Creatine kinase level was tested again, and the result was 1411 IU/L. His kidney functional tests and other routine biochemical tests were normal. HBV-DNA (*deoxyribonucleic acid*) levels have been measured negatively over the past two years. In line with these tests, the patient was admitted to the clinic. Among the autoimmune tests studied during his hospitalization, anti-nuclear antibody, anti-mitochondrial antibody, anti-smooth muscle antibody, and rheumatoid factor tests results were all negative. The erythrocyte sedimentation rate was normal, and the C-reactive protein level was slightly elevated. The patient's neurology consultation was obtained. In the electrophysiological study performed in the neurology clinic, it was reported in accordance with myopathic pattern with normal nerve conduction. Based on the patient's symptoms, physical examination, and biochemical tests, entecavir-induced severe myopathy was thought to be possible and entecavir treatment was discontinued. Three weeks after the drug was discontinued, his serum creatine kinase level was decreased to 235 IU/L. With the improvement in the laboratory, all his clinical symptoms were improved significantly and the patient's exercise capacity increased. The patient was invited to the outpatient clinic at frequent intervals until his condition stabilized and his laboratory findings returned to totally normal.

Discussion

Some cases of myopathy related to the use of clevudine, telbivudine or adefovir have been reported in the literature. In this case report, a rare case of severe myopathy that developed with the use of entecavir during chronic HBV treatment was presented. The distinctive features of the case were muscle pain, loss of strength in the proximal muscles of the lower extremities, and high serum CK (*creatine kinase*) and AST (*aspartate aminotransferase*), ALT (*alanine aminotransferase*) levels. The physical examination and EMG (*electromyography*) characteristics performed in the neurology consultation were very similar to the cases with polymyositis (PM) [5]. But the absence of interstitial lung disease and/or dysphagia in our patient suggested primarily a drug-related side effect.

Entecavir is a nucleoside analog that decreases hepatitis B virus replication. It was approved by the US Food and Drug Administration for the management of chronic HBV in 2005 [6]. Myopathy has often been reported in patients receiving clevudine and telbivudine therapy, but entecavir-associated myopathy is extremely rare.

Zou et al. evaluated the development of myopathy due to telbivudine use and increased CK in a prospective study examining 200 patients, while high CK was observed in 84.3% of the patients, while myopathy was found in only 5% of the patients [7]. The interesting aspect of our case is that when the initial diagnosis of chronic HBV was made, obvious myopathy did not develop despite using telbivudine and severe myopathy developed while using entecavir.

Entecavir-associated myopathy was first reported in 2014 by Yuan et al. [8], in a 44-year-old male chronic HBV patient. Subsequently, very rare cases were reported. Entecavir-associated myopathy can be attributed to mitochondrial toxicity that may develop due to the use of NA [9,10]. In other words, mitochondrial DNA polymerases are also inhibited. Thus, inhibition of mitochondrial functions and finally mitochondrial toxicity triggered by NA's may cause clinically seen overt and sometimes severe myopathy and/or neuropathy [9,10].

Conclusion

Consequently, patients receiving nucleoside analog treatment should be closely screened for many kinds of side effects including myopathy. NA's, as well as entecavir, can induce myopathy in chronic HBV patients. Sometimes it cannot be easy to distinguish cases of myopathy from PM, but detailed analysis and management of all clinical features will help make the correct diagnosis.

Consent for publication: Written informed consent was obtained from the patient.

Conflict of interest: The authors declare that there is no conflict of interest. The authors alone are responsible for the content and writing of the paper.

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