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CASE REPORT

Telbivudine myopathy in a patient with chronic hepatitis B

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Abstract *Case* A 25-year-old man with hepatitis B virus (HBV) infection received antiviral treatment with telbivudine 600 mg daily. Six months after starting treatment, the patient developed progressive weakness and myalgia. Physical examination showed symmetrical proximal weakness. Blood tests at admission revealed positive hepatitis b surface antigen (HBs Ag), and, elevated creatine kinase (CK) level (1,614 U/L, normal range: 38–174 U/L). Aspartate aminotransferase was 64.7 U/L (normal range: 8–40 U/L), and LDH was 293 U/L (normal range: 80–285 U/L). Electrodiagnostic studies indicated myopathic changes. A muscle biopsy revealed myositis and no mitochondrial changes were found. Drug-induced myopathy was suspected and telbivudine was changed to entecavir. The muscle weakness and laboratory findings improved. *Conclusion* A patient developed drug-induced myopathy during long-term treatment with telbivudine for chronic HBV. To promptly detect this reversible adverse event, monitoring of serum CK level and recognition of myopathic signs and symptoms are necessary. Further investigations are needed to clarify the possible mechanism of telbivudine-induced myopathy.

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Keywords Adverse effects · Hepatitis B · Myopathy · Telbivudine

Impact of findings on practice

- Long-term telbivudine treatment may cause creatine kinase elevations and myopathy.
- Muscle enzyme levels should be monitored, and particular attention should be paid to myopathic symptoms and signs.

Introduction

Chronic hepatitis B virus (HBV) infection, a major global health problem affecting more than 360 million people worldwide, is a leading cause of cirrhosis, hepatocellular carcinoma, and liver failure [1]. It is estimated that between 235,000 and 328,000 people die annually due to hepatic cirrhosis and hepatocellular carcinoma, respectively [2]. In recent years, there have been two approved options for treatment. One is interferon therapy, the advantages of which include lack of HBV resistance and a defined duration of therapy. However, its use is limited by its side-effect profile and low response rate [3, 4]. The other strategy is orally administered, well-tolerated, nucleoside or nucleotide analog therapy. It is long-term therapy, and although relapse may occur after stopping therapy and resistant strains of virus can develop, it has expanded the choice of medications for treatment of HBV [3, 4].

Telbivudine is an L-nucleoside analog that is highly selective for and has potent activity against HBV. It is generally well tolerated and superior to lamivudine in

terms of therapeutic response and resistance profile [4]. However, it has been associated with creatine kinase (CK) elevations and myopathy [4]. Myopathy has been reported to occur from 6 to 22 months after telbivudine treatment [5]. The incidence of grade 3/4 CK elevations (≥7.0 times the upper limit of normal) has been reported to range from 7.5 to 12.9 % with myositis occurring in 0.3 to 5 % of patients receiving telbivudine [4, 5]. Until now, most reports have concerned the incidence of CK elevations and myopathy associated with telbivudine [4, 5]. Reports of electromyogram (EMG) and muscle biopsy studies have been rare. We report here on a case of telbivudine-associated myositis confirmed by muscle biopsy.

Case description

A 25-year-old man who received telbivudine therapy for chronic hepatitis B presented with progressive weakness of his extremities over the previous 2 months. The patient had been diagnosed as carrier of HBV 7 years previously. Twenty-eight months previously he had received IFN treatment for 3 months because his alanine aminotransferase (ALT) level was elevated (67 U/L; normal range: 5–40 IU/L) and the HBV DNA level was 7.04×10^7 copies/mL. IFN was stopped because of adverse reactions including hyperthermia and myelosuppression, and he was given lamivudine for 7 months. His ALT level normalized, but the HBV DNA was 2.34×10^4 copies/mL. Lamivudine was changed to adefovir for 10 months, which was also withdrawn because it was not efficacious against the patient's viral load, which increased to 5×10^4 copies/mL. The patient was put on 600 mg of telbivudine once daily and did not take any other medication during the telbivudine therapy. After 4 months of telbivudine therapy, his HBV DNA level had decreased to less than 500 copies/mL. His serum CK level increased to 300 U/L from 98 U/L (normal range: 38–174 U/L), but there was no clinical sign of myopathy. Levels of ALT, aspartate aminotransferase (AST) and lactate dehydrogenase (LDH) were normal. After 6 months of telbivudine therapy, the patient began to experience weakness in his arms when shooting a ball and had difficulty climbing stairs. The weakness progressed and was followed by myalgia in the trunk and extremities, weakness of the neck muscles, palpitations, and lower extremity edema. The patient was admitted for evaluation of the weakness and myalgia. He had a positive Gower's sign, needing his hands and arms to help himself up from a squatting position, and there was tenderness in the biceps brachii, triceps brachii, quadriceps femoris, and the right pectoralis major. He had decreased tendon reflexes, and the proximal muscle strength of the extremities according to the Medical Research Council (MRC) scale was 3/5 (movement against gravity but not against resistance). The distal muscle strength was normal.

Laboratory tests on admission revealed that the CK level had reached 1,614 U/L. Aspartate aminotransferase was 64.7 U/L (normal range: 8–40 U/L), and LDH was 293 U/L (normal range: 80–285 U/L). Levels of ALT, MB isoenzyme of CK, myoglobin and troponin were normal. Tests for serum autoimmune markers (anti-nuclear antibody, anti-double-stranded-DNA antibody, and anti-Jo1 antibody) were negative. Tests for serum tumor markers (alpha-fetoprotein, carcinoembryonic antigen, CA19-9, and CA-125) were all within the normal range. There were no abnormalities on CT scans of the abdomen and pelvis. The electromyography study indicated myopathy with characteristic myopathic discharges on all extremities. A muscle biopsy performed on the vastus lateralis muscle showed multiple regenerating and degenerating atrophic myofibers and numerous necrotic myofibers infiltrated by macrophages on light microscopy (Fig. 1a, b). Staining for myosin ATPase, and nicotinamide adenine dinucleotide-tetrazolium reductase revealed selective type 2 fiber atrophy. Pathologic features indicative of neurogenic or metabolic etiologies were not observed (Fig. 1c, d). An electron microscope examination revealed necrotic fibers. No significant alteration of mitochondria suggestive of mitochondrial myopathy was noted. Telbivudine was discontinued and the patient was switched to entecavir therapy. He was treated with coenzyme Q_{10}, diuretics, vitamin B_1, and vitamin B_{12}. The myalgia and extremity edema were resolved 2 months after discontinuation of telbivudine. The CK level also returned to normal (172 U/L), and muscle strength improved to MRC grade 4/5 (movement against some resistance). The patient regained normal muscle strength by 6 months after telbivudine withdrawal.

Discussion

Telbivudine is a novel, orally administered nucleoside analog that has been developed for use in the treatment of chronic HBV. The multinational GLOBE trial investigated the efficacy and safety profile of telbivudine 600 mg/d (n = 680) compared with lamivudine 100 mg/d (n = 687) over 2 years in patients with chronic HBV [4]. Telbivudine had greater antiviral efficacy than did lamivudine, with an excellent safety and tolerability profile [4]. It was reported during the GLOBE trial that grade 3/4 CK elevations occurred in 12.9 % of the patients treated with telbivudine. Most CK elevations were asymptomatic and transient [4]. Myopathy was reported in 2 of 680 patients receiving telbivudine, both of whom had resolution of symptoms after telbivudine was discontinued [4]. Zou et al. [5] investigated the clinical features and risk factors of CK elevations and myopathy associated with telbivudine in

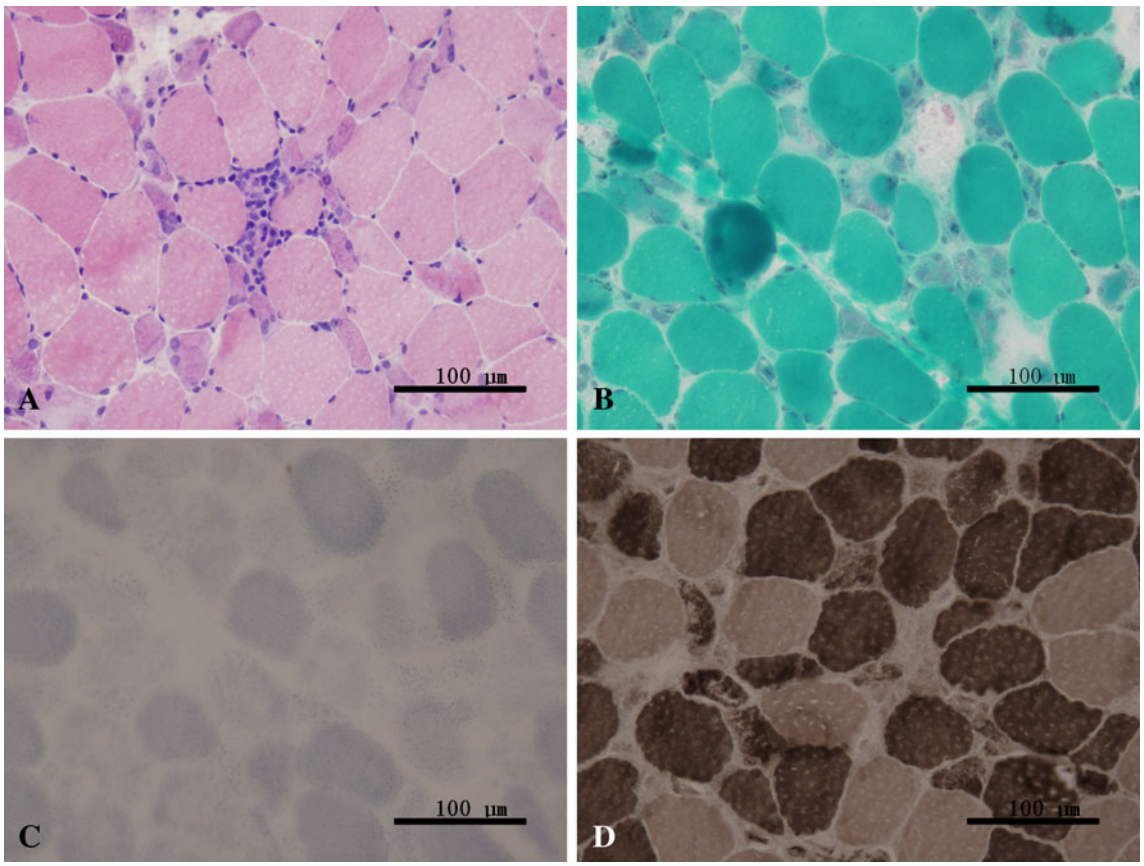

Fig. 1 Muscle biopsy specimen. **a** The muscle biopsy specimen revealed many degenerating and necrotic myofibers with inflammatory cell infiltration. (Hematoxylin and eosin stain; magnification, 400×). **b** The muscle biopsy showed many regenerating and degenerating atrophic myofibers. (Modified Gomori–trichrome stain; magnification, 400×). **c** No mitochondrial alteration suggestive of mitochondrial myopathy was identified. (Succinate dehydrogenase stain; magnification, 400×). **d** Selective type 2 fibre atrophy after staining for myosine ATPase. (Myosin ATPase stain; magnification, 400×)

200 patients with chronic HBV. They observed that CK elevations were common with telbivudine therapy, but myopathy was rare. They suggested that there is a connection between telbivudine and mitochondrial disease. However, no muscle biopsy was conducted.

The patient in the present study developed muscle pain and symmetric proximal limb weakness after 6 months of telbivudine therapy for HBV. There was no clinical or laboratory evidence of myasthenia gravis, autoimmune disease, inclusion body myositis, or paraneoplastic syndrome. The patient's symptoms improved, muscle strength recovered, and serum CK level decreased after discontinuation of telbivudine. Therefore, the link between myopathy and telbivudine therapy in the patient was clear and convincing.

At present, the biological mechanisms of telbivudine-associated CK elevations and myopathy are not clear. It is suggested that they are related to mitochondrial toxicity because evidence of mitochondrial dysfunction has been reported with other nucleoside analogs and skeletal muscle is frequently vulnerable to the effects of mitochondrial malfunction [6, 7]. However, in contrast to other nucleoside analogs, telbivudine has not been associated with inhibition of mammalian DNA polymerase with mitochondrial toxicity [8]. In vitro studies have found that exposure of Human hepatoma HepG2 cells to 10 μM telbivudine for 14 days had no effect on lactic acid production, mitochondrial DNA content, or morphology [9]. Telbivudine at concentrations up to tenfold greater than maximal clinical exposure had no effect on human hepatocytes, skeletal muscle, or neuronal cells, and was not associated with mitochondrial toxicity [10]. In the present case, muscle biopsy showed necrotic myofibers, inflammatory cell infiltration and selective type 2 fiber atrophy. These features are similar to those of steroid-induced myopathy in toxic myopathies. The muscle biopsy did not reveal any mitochondrial changes. These results suggest that other mechanisms may be involved in telbivudine-induced myopathy. It might be associated with oxidative stress, a depletion of any substrate, or disturbance of protein synthesis, like steroid-induced myopathy, which is characterized by myalgia, muscle weakness and increased

CK levels [11]. Because the lack of mitochondrial changes in our results might be related to the timing of the biopsy or the sensitivity of the technique used, we cannot absolutely dismiss the possibility of mitochondrial toxicity.

Conclusion

Our study indicates that long-term therapy with telbivudine may be associated with myopathy. To detect this reversible adverse event without delay, careful clinical evaluations should be accompanied by regular measurements of serum muscle enzymes. Further in vitro and vivo studies are needed to clarify the mechanism of telbivudine-induced myopathy.

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Conflicts of interest None.

References

1. Lavanchy D. Hepatitis B virus epidemiology, disease burden, treatment, and current and emerging prevention and control measures. J Viral Hepat. 2004;11(2):97–107.
2. Perz JF, Armstrong GL, Farrington LA, Hutin YJ, Bell BP. The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide. J Hepatol. 2006;45(4):529–38.
3. Borgia G, Gentile I. Treating chronic hepatitis B: today and tomorrow. Curr Med Chem. 2006;13(23):2839–55.
4. Liaw YF, Gane E, Leung N, Zeuzem S, Wang Y, Lai CL, et al. 2-Year GLOBE trial results: telbivudine is superior to lamivudine in patients with chronic hepatitis B. Gastroenterology. 2009; 136(2):486–95.
5. Zou XJ, Jiang XQ, Tian DY. Clinical features and risk factors of creatine kinase elevations and myopathy associated with telbivudine. J Viral Hepat. 2011;18(12):892–6.
6. Ojetti V, Gasbarrini A, Migneco A, Flore R, Santoliquido A, De Martini D, et al. Lamivudine-induced muscle mitochondrial toxicity. Dig Liver Dis. 2002;34(5):384–5.
7. Seok JI, Lee DK, Lee CH, Park MS, Kim SY, Kim HS, et al. Long-term therapy with clevudine for chronic hepatitis B can be associated with myopathy characterized by depletion of mitochondrial DNA. Hepatology. 2009;49(6):2080–6.
8. Amarapurkar DN. Telbivudine: a new treatment for chronic hepatitis B. World J Gastroenterol. 2007;13(46):6150–5.
9. Standring DN, Bridges EG, Placidi L, Faraj A, Loi AG, Pierra C, et al. Antiviral beta-L-nucleosides specific for hepatitis B virus infection. Antivir Chem Chemother. 2001;12(Suppl 1):119–29.
10. Weaver M, Wolf A, Persohn E, Grenet O, Pognan F. Absence of mitochondrial toxicity of telbuvidine in skeletal muscle cells, hepatocytes, and neuronal cells from rat or human. In: Abstract from the 19th Asian Pacific Association for the Study of the Liver (APASL), February 13–16, 2009, Hong Kong; 2009.
11. Kim BK, Oh J, Kwon SY, Choe WH, Ko SY, Rhee KH, et al. Clevudine myopathy in patients with chronic hepatitis B. J Hepatol. 2009;51(4):829–34.