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Case Report

Rhabdomyolysis happened after the start of dabigatran etexilate treatment: A case report

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Abstract

There are few reports of rhabdomyolysis caused by anticoagulants, and it is extremely rare for it to be caused by dabigatran etexilate. An 86-year-old female experienced sudden muscle weakness and pain, a significant increase in Creatine kinase, and renal impairment after oral administration of dabigatran etexilate for 3 weeks. The enhanced thigh MRI showed abnormal signal in multiple thigh muscle groups, indicating that the lesions should be considered inflammatory diseases. In conclusion, the possibility of rhabdomyolysis should be ruled out when muscle weakness and myalgia occur at the beginning of dabigatran etexilate treatment.

Keywords: Dabigatran Etexilate, MRI, Muscle Weakness, Myalgia, Rhabdomyolysis

Introduction

Approximately 20-30% strokes are caused by atrial fibrillation[1].Anticoagulantmedicationsarethecoretherapeutic measures. As one of novel oral anticoagulants(NOACs), the safety and effectiveness of dabigatran etexilate in preventing stroke in patients with non-valvular atrial fibrillation (NVAF) have been widely recognised[2].

The main adverse reaction of dabigatran etexilate is hemorrhage[3]. Others include esophagitis or esophageal injury, impairment of hepatic and renal function, myocardial infarction or acute coronary syndrome, as well as allergic reactions, etc[4].

Rhabdomyolysis is the most serious form of myopathy, caused by striated muscle injury releasing toxic intracellular substances into peripheral blood[5]. From asymptomatic elevation of creatine kinase (CK) to symptoms such as fatal arrhythmia, acute renal failure (ARF) and disseminated intravascular coagulation (DIC), can occur in rhabdomyolysis[6].

We describe a case of rhabdomyolysis with characteristic MRI findings after oral administration of dabigatran etexilate, which had never been reported before.

Case presentation

The patient was an 86-year-old female with diabetes, and a long history of atrial fibrillation. She taken acarbose (0.1 g BID) and gliclazide (60 mg QD) for her diabetes. In addition, she received long-term anticoagulation and not on statin treatment. The warfarin was replaced with dabigatran (110 mg BID) because of gastrointestinal bleeding 21 days ago. Subsequently, the patient woke up in the morning with sudden weakness in limbs, accompanied by muscle stiffness and pain in both lower limbs, inability to stand. The similar symptoms never occurred before and no traumatic event had happened to her. She was admitted to the hospital the next day with increased weakness of both lower limbs. Neurological examination showed a mild grade 4+/5 weakness of bilateral lower limbs weakness, normal muscle tone, and a negative bilateral Babinski sign. Laboratory test showed: aspartate transferase (AST) level was 158 u/L, alanine aminotransferase (ALT) was 45 U/L, CK was 3931 U/L, uric acid (UA) was 581.6 μmol/L, creatinine was 120.09 μmol/L, and urea nitrogen (BUN) was 12.14 mmol/L (Figure 1); Hepatitis B surface antibody was positive and other hepatitis antibody was negative; Peripheral blood cells and

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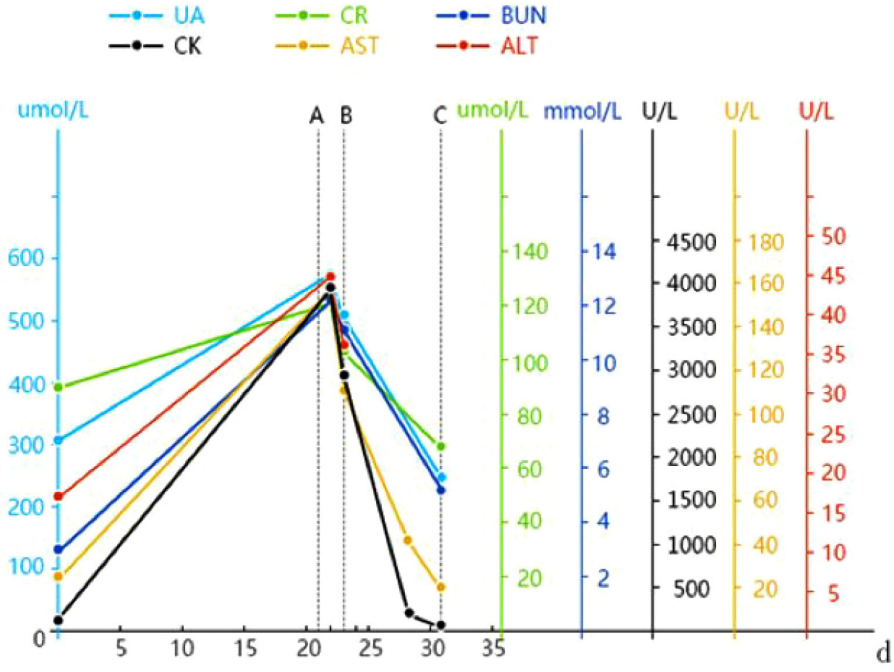

Figure 1. Changes of creatine kinase, liver and kidney function indices before and after taking dabigatran etexilate discontinuation. A: The onset of dabigatran etexilate-related symptoms occurred 21 days after taking it, and myasthenia and myalgia began to appear. B: Dabigatran etexilate was discontinued on the 23rd day. The patient had muscle weakness and myalgia, CK, ALT, AST, CR, BUN, and UA were all elevated. C: 8 days after the drug withdrawal, the patient's myalgia, muscle weakness were basically relieved. CK, liver and kidney functions returned to normal. Reference value: CR (45-84) μmol/L, BUN (2.9-8.2) mmol/L, UA (155-357.0) μmol/L, CK (26-140) U/L, AST (13-35) U/L, ALT (7-40) U/L.

hs-CRP were normal; The urine color was generally normal. The enhanced magnetic resonance imaging (MRI) of thigh showed bilateral diffuse signal abnormalities in thigh muscle; T2 fat suppression showed hyperintense signal, and after T1-weighted enhancement, the thigh lesion showed patchy abnormal enhancement (Figure 2). B-ultrasound revealed no obvious masses on the inner thighs of both lower limbs. She was diagnosed with rhabdomyolysis.

Dabigatran etexilate was discontinued one day after admission to hospital. After that, the patient's symptom of myalgia and muscle weakness were significantly relieved, and CK levels gradually decreased. After 8 days of discontinuation, the CK level dropped to 71 (U/L) (Figure 1). Moreover, the patient was continue taking other drugs for the continuing care of other chronic diseases before and after rhabdomyolysis. We adopted Naranjo score to assess the causality of adverse drug reactions, and the Naranjo score was 6 (Table 1)[7]. The score indicates that dabigatran etexilate lead to rhabdomyolysis probably.

Discussion

As one of the new oral anticoagulants, dabigatran reduces thrombosis by inhibiting thrombin activity directly and reversibly, and is widely used in the treatment of NVAF and pulmonary embolism[8]. There are few reports of rhabdomyolysis caused by anticoagulants, except for the combination of warfarin and atorvastatin or simvastatin treatment[9,10]. To our knowledge, dabigatran etexilate-induced rhabdomyolysis has not been clinically reported. We provide an interesting case suffering from muscle weakness and pain after taking dabigatran etexilate for 3 weeks, and the symptoms relieved rapidly 8 days after dabigatran etexilate withdrawal.

Pathogenic causes of rhabdomyolysis include excessive exercise, trauma, metabolic disorders, poisons, extreme body temperature, and infections. In addition, the iatrogenic cause of rhabdomyolysis mainly refers to drugs especially the statin treatments[11,12]. The typical clinical manifestations of rhabdomyolysis are muscle soreness, weakness, and brown urine[13]. Acute kidney injury is the most common systemic complication of rhabdomyolysis (incidence rate is 10-55%) and with unfavourable prognosis[14]. A diagnostic criterion for rhabdomyolysis is defined to 5 times the upper limit of normal for CK (>1000 U/L)[15-18]. The current patient's CK was 28 times the upper limit of normal. Moreover, CR, AST, ALT, and other indicators were also elevated (Figure 1), which is consistent with the diagnosis of rhabdomyolysis. Interestingly, after 8

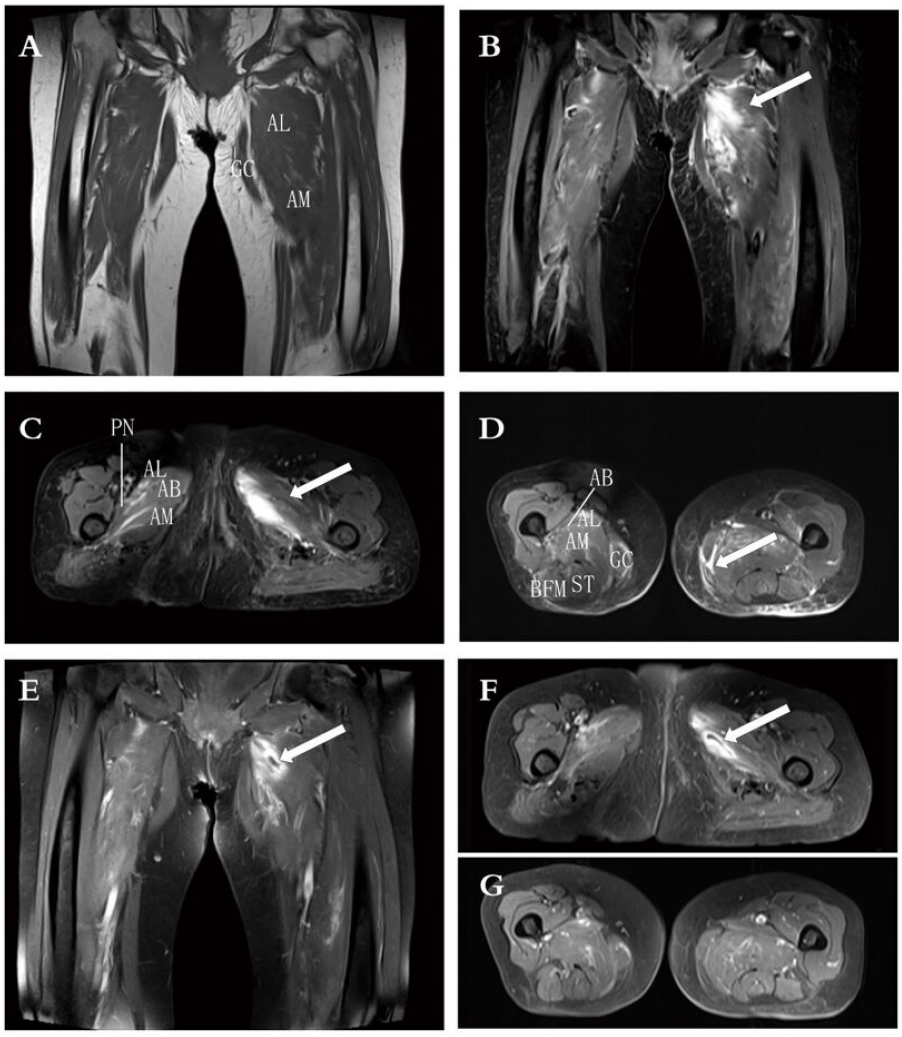

Figure 2. Bilateral thigh enhanced MRI on the 4th day after drug discontinuation in an 86-year-old woman. (A) coronal T1W images showed isosignal and blurred muscle space; coronal T2 fat suppression (B) and axial T2 fat suppression (C, D) images showed diffuse hyperintensities (arrow), including bilateral adductor longus (AL) muscle,adductor brevis (AB) muscle, adductor magnus (AM) muscle,gracilis muscle (GC) ,biceps femoris muscle (BFM), semitendinosus muscle (ST) and muscle space, and the lesion boundary was not clear. In coronal T1W image enhancement (E) and axial T1W image enhancement (F, G), the lesions showed diffuse patchy obvious enhancement, local visible non enhancement area, indicating local necrosis (arrow).

days of discontinuation of dabigatran etexilate cessation, the patient's muscle weakness and pain were relieved, and the CK, liver enzymes, and renal function indices returned to normal (Figure 1). During this period, other medications for this patient remained unchanged. Additionally, CK, CR, and other related indicators were basically normal before dabigatran etexilate treatment (Figure 1), which supported the diagnosis further. The Naranjo score indicates that dabigatran etexilate lead to rhabdomyolysis probably.

T2-weighted MRI is an impactful technique to evaluate rhabdomyolysis, showing reversibility high intensity in the involved muscle groups. This indicates transient edema and inflammation in the acute phase of rhabdomyolysis, not permanent myopathic changes[19]. Gadolinium-enhanced T1-weighted imaging can be used to distinguish between chronic and acute lesions[20]. There are two imaging types of rhabdomyolysis. Type 1 is mostly caused by overexertion and the imaging features of affected muscles include homogeneously isointense to hyperintense on T1 weighted, homogeneously hyperintense on T2-weighted and and homogeneously enhancement on contrast-enhanced MR images. However, type 2 rhabdomyolysis show heterogeneously or homogeneously isointense to hyperintense on T1-weighted, heterogeneously hyperintense on T2-weighted images, and rim enhanced on contrast-enhanced MRI[21]. In the current patient, the T2-

Table 1. Naranjo adverse drug reaction causality scale scores.

Question	Score
1. Are there previous conclusive reports on this reaction?	0
2. Did the adverse event appear after the suspected drug was administered?	+2
3. Did the adverse event improve when the drug was discontinued or a specific antagonist was administered?	+1
4. Did the adverse event reappear when the drug was readministered?	0
5. Are there alternative causes that could have caused the reaction on their own?	+2
6. Did the reaction reappear when a placebo was given?	0
7. Was the drug detected in blood or other fluids in concentrations known to be toxic?	0
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	0
10. Was the adverse event confirmed by any objective evidence?	+1
Total score	6
Probability of ADR(adverse drug reaction): ≥9 (Definite); 5-8 (Probable); 1-4 (Possible); ≤0 (Doubtful).	

weighted fat suppression image showed heterogeneously hyperintensities, and patchy abnormal enhancement was observed on contrast-enhanced MRI (Figure 2), which is consistent with the previous report and belong to type 2 rhabdomyolysis due to drug[21,22].

Previous reports have shown that dabigatran etexilate itself can damage hepatic or renal function, but it is uncommon. A 59-year-old patient showed a significant increase in CR after 4 weeks of dabigatran etexilate treatment. The kidney biopsy revealed diffuse tubulointerstitial nephritis[23]. Another patient developed progressive painless jaundice and increased liver enzymes after taking dabigatran etexilate for 2 weeks, and these symptoms relieved gradually after dabigatran withdrawal and symptomatic therapy[24]. The current case was characterized by both impairment of hepatic and renal function. Combined with MRI results and clinical symptoms, it may be related to rhabdomyolysis induced by dabigatran etexilate.

In summary, our case showed rhabdomyolysis which may be caused by dabigatran etexilate. Thus, in the early stage of dabigatran etexilate treatment, once limb weakness occurs, CK should be tested to rule out the possibility of rhabdomyolysis. Contrast-enhanced muscle MRI showing high bilateral diffuse signal will offer help to the qualitative diagnosis of rhabdomyolysis.

Ethical approval

This paper was approved by the Ethics Committee of the first affiliated hospital of Zhejiang Chinese Medical University, with the ethical approval number (2020-KL-167-03). Due to the retrospective study, informed consent was waived.

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