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Lamotrigine-Induced Lupus-Like Syndrome: A Case Report and Literature Review

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Lamotrigine, as a new generation anticonvulsant, has been widely used in treating epilepsy. It is also a mood stabilizer for bipolar disorder. Common adverse effects include nausea and vomiting, dyspepsia, insomnia, somnolence, and rash. However, drug-induced lupus (DIL) due to lamotrigine has been rarely reported. We report a case of lupus-like syndrome associated with lamotrigine. A 39-year-old male developed arthralgias and positive serum antinuclear antibody repeatedly with introductions of lamotrigine. The strong temporal relationship between the rheumatological features and drug exposure is illustrative of the disease course of DIL. Two hitherto reported lamotrigine-related DIL cases are compared with our case.

Keywords: lamotrigine, drug-induced lupus, epilepsy, adverse effect

INTRODUCTION

Lamotrigine is a selective voltage-dependent sodium channel blocker. It has become a popular antiepileptic drug since its introduction into the market in 1990s. It is also indicated as mood stabilizer in treating bipolar disorder. Common adverse effects included headache, drowsiness, insomnia and somnolence, nausea and vomiting, and rash. Lupus syndrome induced by this drug is rare.[1] We report a case of lamotrigine-induced lupus-like syndrome, presented with arthralgias and raised antinuclear antibodies (ANA) titers.

CASE REPORT

A 39-year-old male presented with arthralgias for about a year in November 2009 (Table 1). He had a history of idiopathic generalized epilepsy diagnosed at the age of 13. His seizure semiology was described as generalized tonic clonic on diagnosis. Electroencephalography demonstrated generalized 3-Hz spike and slow wave complexes. Magnetic resonance imaging of the brain showed no lesions. His epilepsy had been reasonably controlled by phenytoin for about 20 years until 2006 when he complained of increasing breakthrough attacks. Lamotrigine was prescribed to replace phenytoin. The patient had otherwise no major health problem. His family history was remarkable, for his father and brother both had autoimmune neutropenia.

The joint pain involved the wrists, elbows, and right hip. There was also joint swelling and redness. The symptoms fluctuated with the joint pain could affect his daily living on some of the days but almost completely resolved a few days afterward. There were no skin rashes, oral ulcers, photosensitivity, or Raynaud phenomenon. His ANA was positive at a dilution of 1:1280 in a homogeneous pattern compared with the baseline of 1:256 in a speckle pattern checked previously as part of epilepsy workup. Antidouble stranded DNA (anti-dsDNA) antibody was negative, but anti-Ro/SSA antibody was positive. Rheumatoid factor was negative. His blood picture, renal and liver function tests, and urine analysis findings were normal. Lamotrigine dose was 600 mg/d, and the drug serum level was within a therapeutic range of 12.0 mg/L (reference range 4.0–18.0 mg/L) at that

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Table 1. Clinical course of our patient, his medication, and ANA levels.

Date	Antiepileptic drug use (daily dosage)	ANA titer (pattern)	Remarks
1985	PHT	1:256 (S)	Diagnosis of IGE
2006	Switched from PHT to LTG		Suboptimal seizure control
November 2009	Switched from LTG (600 mg) to PHT	1:1280 (H)	Arthralgias for 1 yr; suspected DIL. Joint symptoms completely resolved within 2 mos after stopping LTG
February 2010	PHT	1:320 (H)	
May 2010	Switched from PHT to LTG (300 mg)		Intolerable dizziness due to PHT
June 17, 2011	Began switching from LTG to PHT	1:1280 (H)	Recurrent arthralgias for 6 mos
June 21, 2011	Started VPA and tailing off LTG		Admitted for convulsions with absence status
August 2011	VPA (1500 mg), tailing off LTG	1:1280 (H)	Arthralgias completely subsided
December 2011	VPA (1500 mg)	1:640 (H)	

H, homogeneous; IGE, idiopathic generalized epilepsy; LTG, lamotrigine; PHT, phenytoin; S, speckled; VPA, valproic acid.

time. Drug-induced lupus (DIL) was suspected. He was switched back to phenytoin. ANA titer dropped to 1:320 in a homogeneous pattern 2 months later.

However, he complained of intolerable dizziness with phenytoin. Lamotrigine was resumed at the patient's preference in May 2010. Lower dose of 300 mg/d was given. Again, the arthralgias recurred 1 month later, and the ANA titer climbed up to 1:1280 in homogeneous pattern. Other blood tests results remained stable. Serum lamotrigine level was 11.6 mg/L. He was scheduled to switch back from lamotrigine to phenytoin at that juncture. But a few days after the decision, he was admitted to our unit for absence status epilepticus. Valproic acid was started instead of phenytoin. Lamotrigine was tailed off slowly. His seizures were then satisfactorily controlled. Anti-dsDNA on recheck was positive at 1:40 while the patient was weaning lamotrigine despite the arthralgias resolved completely several weeks after the step-down. ANA titer dropped to 1:640 4 months after stopping lamotrigine completely.

DISCUSSION

There are currently no well-established diagnostic criteria for DIL syndrome.[2,3] Our patient has only 3 out of the 11 diagnostic criteria of systemic lupus erythematosus (SLE) by the American College of Rheumatology, including arthritis, abnormal ANA, and anti-dsDNA titers.[4] The seizure disorder, which occurred many years before the emergence of the rheumatological syndrome and was not associated with abnormal imaging findings, is not considered to be of autoimmune cause. Our patient showed consistent temporal relationships among symptoms, ANA titers, and lamotrigine use: He developed arthralgias and high ANA titer while on lamotrigine; with discontinuation, symptoms resolved and ANA titer dropped; on rechallenge, symptoms recurred and ANA titer rose; again on discontinuation, symptoms resolved and ANA titer dropped afterward.

It is well known that DIL has different clinical features compared with SLE and often does not fulfill the diagnostic criteria of SLE.[2] Typical malar or discoid rash, photosensitivity, oral ulcers, alopecia, nephropathy, and neurological disorders are uncommon in DIL. Arthritis, myalgia, fever, and serositis are frequent presenting symptoms instead. Also, the symptoms of DIL are generally less severe than SLE and tend to resolve on the withdrawal of the offending drugs. Positive anti-dsDNA is relatively uncommon in DIL but is not excluding.[3] Delayed serological improvement is possible.[5] Family history of autoimmune disease may predispose our patient to DIL.

There have been only 2 case reports of lamotrigine-induced SLE in the literature to our knowledge.[6,7] They both had at least 4 out of 11 of clinical features of ARC definition of SLE. Both cases did not develop symptoms shortly after initiation of lamotrigine. One case occurred after >1.5 years and the other >2 years. Our patient complained of arthralgias about 2 years after starting lamotrigine. This is compatible with the typical DIL in which symptoms usually emerge weeks to years after the use of the offending drugs.[2] The prescribed lamotrigine doses in the previous 2 cases were not high. In the first case, a 57-year-old woman was given 2 $mg \cdot kg^{-1} \cdot d^{-1}$ and in the second cases, an 18-year-old lady was on 300 mg/d. Our patient was on a relatively high dose of 600 mg/d at the first presentation, but the lupus-like features recurred while on a smaller dose of 300 mg/d. The drug levels were not in toxic ranges at times of exacerbation. These probably imply that DIL due to lamotrigine is not necessarily related to high dosage or toxic serum drug level. The rheumatological features of our patient recurred relatively shortly of 6 months after rechallenge by the lamotrigine at lower dose. Whether it is resulted from the sensitization of the immune system by the first encounter is subjected to further studies.

CONCLUSIONS

Other antiepileptics that can cause DIL include carbamazepine, phenytoin, valproate, ethosuximide, trimethadione, primidone, and zonisamide.[2,8,9] The symptoms of DIL are readily reversible by drug withdrawal. Being vigilant to the clinical and immunological features is the most important in the management of this uncommon syndrome, no matter how long the treatment period has been or what the dosage of the drug is.

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