Cross-sensitivity of Levetiracetam and Carbamazepine Induced Skin Rash

Samhita Panda

Abstract

Antiepileptic drugs (AEDs) are fairly commonly associated with drug induced rash that can be mild to life threatening. Aromatic AEDs are often linked to these skin reactions unlike newer non-aromatic ones such as levetiracetam (LEV), lacosamide and zonisamide. Drug rash including drug-induced hypersensitivity syndrome is a rare complication of LEV use. We report a case of maculopapular skin rash due to LEV with cross-sensitivity with CBZ which has not been reported till date.

Introduction

Drug induced rash is a common adverse effect of antiepileptic drugs (AEDs).[1] The AED-induced skin reactions vary from benign urticaria, maculopapular eruptions and acute generalized exanthematous pustulosis to more life-threatening conditions like toxic epidermal necrolysis (TEN), Steven Johnson Syndrome (SJS) and drug reaction with systemic symptoms syndrome (DRESS).

Most of the skin reactions occur in relation to aromatic AEDs such as phenytoin (PHT), carbamazepine (CBZ) and phenobarbitone.[2-4] While most implicated AEDs belong to the older generation, some of the newer ones such as oxcarbazepine (OXC) and lamotrigine (LTG) are also frequently linked to skin reactions. Compared to these, valproate (VPA), levetiracetam (LEV), lacosamide and zonisamide (ZSM) are rarely associated with skin related adverse events. Till date, there are only a few case reports of LEV-induced skin rash including DRESS.[5-9] Here, a case of maculopapular skin rash, most probably an adverse effect related to LEV exposure with cross-sensitivity with CBZ is reported.

Case Report

A 35-year-old lady presented with two episodes of generalized tonic-clonic seizures 4 months apart. There was brief cephalic aura following which she had behavioural arrest, eye and head deviation to left and stiffening of body. Electroencephalograph showed intermittent diffuse cerebral dysrhythmia, more over the right hemisphere. Magnetic resonance imaging showed only asymmetric dilatation of right temporal horn without any evidence of mesial temporal sclerosis. She was initiated on CBZ with gradual up-titration to dose of 600 mg per day. Apart from initial sedation, she did not have any recurrence of seizures. She reported after 8 weeks with slowly progressive maculopapular, pruritic rash over the body for 12 days. She had consulted a dermatologist 2 days prior to visit and had been suggested the possibility of CBZ-induced drug rash. On examination, there was a red, maculopapular rash over the face, neck, limbs and torso which was confluent at places (Figure 1). There were no pustules or lesions involving the mucosa, palms or soles. There was no periorbital or perioral edema. Abdomen was soft and no hepatosplenomegaly was noted. Chest examination was non-contributory. Complete blood count showed hemoglobin- 13.7 g/dl, total leucocyte count- 10,800/ cu mm and absolute eosinophil count- 326/ µL (normal 100-1000/µL). The Naranjo score was 6. Considering a late-onset CBZ-induced drug rash, CBZ was stopped. She was treated with steroids, antihistaminics and topical steroids.

LEV was started in view of its relative safety. The rash subsided completely. However, she re-visited after 4 weeks with re-appearance of pruritic, maculopapular rash over limbs and face with desquamation of skin over the groin folds. No mucosal involvement or periorbital swelling was noted. The IgE level was 57 KIU/L (normal<150 KIU/L). Naranjo score was 7. Since the patient was on no other medication, LEV was implicated for the drug rash and early TEN. It was stopped and she was subsequently put on Clobazam on which she has remained seizure free for the past 3 years.

Discussion

Hypersensitive skin reactions to AEDs have been known since first reports by Silber et al in 1934.[2] The spectrum includes benign conditions such as urticaria, maculopapular eruptions and acute generalized exanthematous pustulosis, to serious dermatologic disorders namely SJS, TEN and DRESS or drug induced hypersensitivity syndrome (DIHS).[3] TEN is characterized by erythema, bullous detachment and necrosis of the epidermis and mucous membranes, sepsis and even death. SJS is characterized by fever, flu-like symptoms, blistering and peeling of skin, sepsis, dehydration and multiple organ failure. SJS involves less than 10% of the body surface unlike TEN which involves more than 30%. DRESS or DIHS, first described with phenytoin and named by Bouquet comprises of rash, fever, swelling, eosinophilia and organ dysfunction effecting the liver, kidneys, heart or lungs. Compared to SJS and TEN, hypersensitivity syndrome has less remarkable mucosal involvement.[1] The mortality is 4% in SJS, 10% in DRESS and 30% in TEN.

Drug induced skin reactions occur in upto 10% patients on at least one AED.[1,4] In a retrospective study on 300 patients with epilepsy, 95% of hypersensitive reactions occured with CBZ, PHT, LTG and OXC with 86% observed less than 3 months after initiation of medicines. Elderly patients and those of female gender had higher risk to develop drug reactions. Non-aromatic drugs such as VPA, LEV, vigabatrin and topiramate were rarely associated with skin rash.[1] Amongst the newer

Associate Professor, Department of Neurology, All India Institute of Medical Sciences, Jodhpur, Rajasthan
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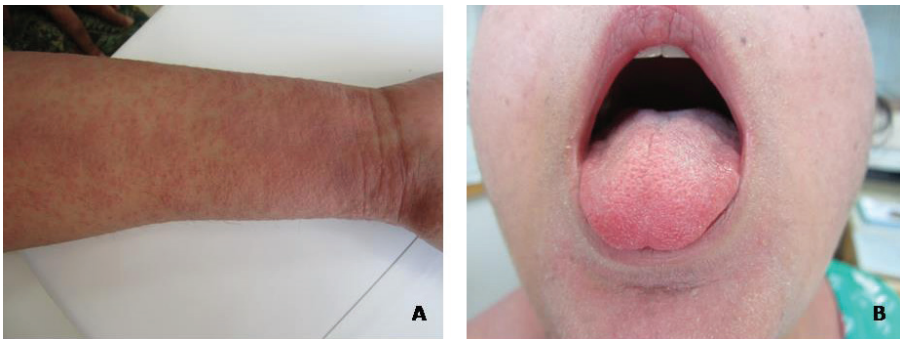

Fig. 1: Maculopapular reddish exanthematous eruption over A. The limbs and B. Perioral regions, sparing mucosal membranes

AEDs, LTG is the exception with high incidence of drug hypersensitivity. Rarely, VPA co-medication with LTG may be a risk factor for drug rash due to the inhibition of uridine diphosphate glucuronyltransferase.[10]

The present case exemplifies the rare situation of LEV-induced generalized exanthema occurring as cross-sensitivity to CBZ. LEV is a pyrrolidine compound with unclear mechanism of action. It does not influence the voltage gated sodium channels, GABA mediated transmissionor calcium currents. It may regulate exocytosis and neurotransmission by binding to the synaptic vesicle protein 2A in the synaptic plasma membranes in the central nervous system. It selectively prevents hyper-synchronization of epileptiform burst firing and propagation of seizure activity without affecting normal neuronal excitability.

Like valproic acid, LEV has low frequency of rash compared to PHT, CBZ, LTG and ZSM in a retrospective study on 15 AEDs.[4] Only a few scattered case reports on LEV-induced rash are present in literature.[5-9] Overall, only 0.8% of patients develop rash after LEV. On rare occasions, drug induced skin reactions have occurred after introducing LEV as a substitute for rash due to other AEDs.[6,9] One patient, who had already experienced maculopapular skin rash with lamotrigine and phenytoin given sequentially, developed rash with angioedema after the first dose of LEV.[6] Similar eruption of morbilliform, pruritic rash after LEV was noted in another patient who had previous rash due to combination of pheytoin and oxcarbazepine.[9] Our patient is the third such case demonstrating cross-sensitivity to another aromatic AED, i.e. carbamazepine. In a study of 3793 consecutive Chinese patients with epilepsy, 3.61% (137) developed rash and only 18 patients had rash to two or more AEDs.[11] High rates of cross reaction was noted amongst aromatic AEDs, specifically CBZ and PHT, CBZ and LTG and CBZ and OXC unlike with LEV.[11,12]

While most drug hypersensitivity syndromes are idiosyncratic and not dose related, some of the drug reactions have a genetic basis. As such, the increased risk of drug reaction may be informed to the first degree relatives. Once having a drug hypersensitivity, one should avoid other aromatic AEDs and opt for non-aromatic compounds. However, in rare circumstances as in our case, a safe option like LEV may produce such a hypersensitive exanthema. Desensitization by gradual dose excalation and using other alternatives such as clobazam and mast cell stabilizers may be done.

Conclusion

Levetiracetam with its unique mode of action in focal and generalized epilepsies is a major component of antiepileptic drug armamentarium which has been considered relatively safe compared to older AEDs. However, recent reports have shed light on adverse effects not previously documented. Drug rash is a rare complication of LEV use and substitution with LEV should be done slowly under supervision in patients who previously developed AED induced rash.

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