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Levetiracetam Induced Cutaneous Side Effects: Case Report

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ABSTRACT

Background: Many drugs have been successfully used for the treatment of epilepsy. However, medications related complications are usually inevitable. The aim of the work was to report the limited rare cutaneous manifestations associated with Levetiracetam (LEV); a commonly used anti-epileptic drug (AED). Two cases were reported with literature review. **Method:** This is a retrospective case report enrolling two patients with primary generalized epilepsy who developed different cutaneous manifestations that were previously reported in the literature on minimal occasions. **Conclusion:** LEV is not known to induce cutaneous manifestations, and if occurred, it would be dose-related. Therefore, utmost care should be taken when prescribing LEV dosage to avoid such complication.

INTRODUCTION

Epilepsy is one of the commonly encountered neurological diseases in medical practice. The prevalence of the disease in Saudi Arabia is about 6.5 per 1000 [1]. Different types of epilepsy do exist, including generalized onset, focal onset, combined or unknown [2].

Generalized onset epilepsy is having many tools for treatment including pharmacological treatment. LEV is one of the widely used medication for the treatment of epilepsy [3]. Its complications are limited and mostly rare [4]. Recently, some literature reported cutaneous complications as a rare side effect of this drug.

In the present case study, we are reporting two cases of LEV related cutaneous complications in the form of hyperpigmentation of the skin and maculopapular rashes that have been discussed based on the literature data.

CASE #1

A 25-year-old female patient was diagnosed with primary generalized epilepsy seven years ago. She has been on topiramate since the beginning of her treatment regimen until she was presented at the clinic complaining from paresthesia and psychomotor slowing symptoms and asking for other AED choices if possible. Discussion about the risk of breakthrough attacks and risk of status epilepticus was initiated. However, her preference was to switch to alternatives considering her preference and her marital status as she is married. For which, slow taper down plan of topiramate was discussed with her and LEV was selected to be initiated. LEV was prescribed in a dose of 500mg BID for one week along topiramate slow taper down plan. After two weeks, her LEV was reached 1000mg BID. She continued using the same dose for two days till she noticed skin changes over her upper limbs bilaterally. Therefore, she was presented to outpatient clinics to seek a medical opinion. She was referred immediately by a family physician to our clinic. She was on LEV 1000mg BID and end of taper-down of topiramate with a dose of 25mg BID at that time. Her skin lesion manifested as a maculopapular rash over her forearms and abdomen mainly.

Her history and medications were reviewed and were not remarkable for any obvious causes. The suspension of LEV induced skin rash is raised and considered. Consequently, topiramate was started, and LEV was discontinued. We admitted in the ward was under observation and for symptomatic management. Her rashes resolved after 24 hours.

CASE #2

An 18-year-old female patient has been diagnosed with primary generalized epilepsy for 16 months.

She was treated with sodium valproate (VAD) in another hospital. Then, we shifted to LEV when presented to our clinic because of VAD side effects. Initial Levetiracetam dose was 500mg TWICE daily then she was kept on 750mg TWICE daily for about six months.

Due to breakthrough seizures, we increased her dose to be 1000mg TWICE daily. After seven days from the new dose initiation, she started to notice skin changes over her hand bilaterally. She did not stop AED, and she was presented to the emergency department and a very near appointment with neurology clinic was set up. She presented to the clinic with hyperpigmentation skin changes over dorsal surfaces of her hands bilaterally at day 12 after new dose initiation. There were noticeable early similar skin changes over her feet bilaterally which were not noticed by the patient. The skin changes involved about 10% of body surface area. Her rash was managed accordingly. LEV has been replaced by topiramate successfully without seizure recurrence or rash. Her condition improved gradually.

DISCUSSION

Hyperpigmentation is darkening of the skin, mucous membranes, or nails that may result from a variety of causes like sun exposure injuries, infections, autoimmune diseases, contact dermatitis, photosensitivity, or allergic reactions [5]. It has been reported that medications are the cause in 10 to 20% of patients with acquired hyperpigmentation [6]. The level of evidence supporting a causal relationship

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between hyperpigmentation and medication use is mainly derived from case reports [5]. Allergic reactions are generally categorized as immediate or non-immediate onset type, with the latter being more frequent[7]. Maculopapular rash is one of the most common presenting findings in allergic reactions cases.

Meta-analyses in the literature showed that AEDs had aggression as a side effect, and the behavioral side-effect profiles of AEDs should be considered when choosing optimal AEDs [8].

In literature, there are some cases of multiple skin changes have been linked to LEV, and they showed improvement after discontinuation and management. Cutaneous side effects following anti-epileptic drugs (AED) described in the literature that might be more linked to phenytoin, phenobarbital, carbamazepine, oxcarbazepine and lamotrigine [9].

In general, medication side effects can range from simple reversible effects to a life-threatening stage, including cutaneous reactions. In our two cases, what we noticed that their cutaneous changes were dose-dependent. Although Immune-mediated drug reactions are thought to be dose- independent, some reports discussed the hypothesis of dose-dependent cutaneous reactions specially titration rate [10]. The relationship between starting dose and titration rate in cutaneous drug reaction is particularly notable with some AED like lamotrigine and carbamazepine [11]. Aging and female gender seems to increase the risk of skin rashes [12]. Although no AED is free from the potential of inducing idiosyncratic reactions, the magnitude of risk and the most common manifestations vary from one drug to another, a consideration that impacts on treatment choices [10]. Some different phenotypes were described in the literature like a psoriasiform lesion that appeared at day ten after LEV first dose [13]. No clear association between LEV cutaneous side effects and HLA genes, Fa-Yun Hu et al. reported [15]. In our cases, skin changes have been linked to LEV due to lack of other causative agents neither infectious nor other medication usages. No known history of allergic reaction to any medications or food in both cases. The treatment of drug-induced skin hyperpigmentation consists of interruption of the causative drug mainly. In most of the situations, an optimal resolution is often achieved. However, the hyperpigmentation may persist for an extended period or may become permanent in a small number of patients [14].

CONCLUSION

The presented cases highlight the hypothesis of dose-dependent cutaneous side effects following LEV that could be immediate or non-immediate reactions. Continuous monitoring and observation for immediate and non-immediate reactions should be considered alongside patient education.

Further studies are recommended to determine possible risk factors either genetic or non-genetic ones.

Until now, it is deemed to be rare to see such side effects following LEV, but if any, immediate intervention should be performed accordingly.

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