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DRUG REACTION WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS SYNDROME INDUCED BY LEVETIRACETAM IN A PEDIATRIC PATIENT

Ayşe Kaçar Bayram, MD,* Mehmet Canpolat, MD,* Salih Levent Çınar, MD,† Fulya Tahan, MD,‡ Hakan Gumus, MD,* Sefer Kumandaş, MD,* and Hüseyin Per, MD*

*Department of Pediatric Neurology, Erciyes University Medical School, Kayseri, Turkey, †Department of Dermatology, Erciyes University Medical School, Kayseri, Turkey, and ‡Department of Pediatric Allergy, Erciyes University Medical School, Kayseri, Turkey
Corresponding Address: Ayşe Kaçar Bayram, MD, Department of Pediatric Neurology, Erciyes University Medical School, 38039, Melikgazi, Kayseri, Turkey

☐ **Abstract—Background: Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a rare, life-threatening hypersensitivity drug reaction. Patients present with cutaneous rash, fever, lymphadenopathy, hematologic abnormalities with eosinophilia and atypical lymphocytes, and visceral organ involvement. The prognosis of DRESS syndrome is related to the degree of end-organ damage, and the mortality rate is approximately 10%. Case Report: We report a 9-year-old girl treated with only levetiracetam because of intracranial space occupying mass-related seizures. The patient developed pharyngitis accompanied by exudative membrane, bilateral cervical lymphadenopathy, tender hepatomegaly, skin rash, and fever after 19 days of levetiracetam therapy. Laboratory findings revealed leukocytosis, lymphocytosis with an atypical lymphocytosis, eosinophilia, thrombocytopenia, and elevated serum transaminases. Serologic studies of viruses were negative. The patient was diagnosed with DRESS syndrome and antiepileptic therapy was ceased immediately. The systemic signs and symptoms of the patient were improved after systemic steroid and antihistamine therapy. Why Should an Emergency Physician Be Aware of This?: It is important that emergency physicians be aware of the possibility of DRESS syndrome when attending children that present with clinical viral infections. We would like to emphasize that obtaining a careful and detailed medication history is an essential part of clinical assessment for the diagnosis of DRESS syndrome.** © **2016 Elsevier Inc.**

☐ **Keywords—antiepileptic-induced hypersensitivity reaction; child; DRESS syndrome; drug reaction; levetiracetam**

INTRODUCTION

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a rare, life-threatening hypersensitivity reaction associated with many different medications. The clinical features of this syndrome include cutaneous rash, fever, lymphadenopathy, hematologic abnormalities with eosinophilia and atypical lymphocytes, and ≥1 visceral organ involvement, such as hepatitis, nephritis, interstitial pneumonitis, pancreatitis, or myocarditis (1–3). The mortality rate is approximately 10% and is most commonly caused by to liver failure. Multiorgan involvement is associated with a higher rate of mortality (1,3). Diagnosis is generally made according to the clinical features and biochemical investigations. The severe Cutaneous Adverse Reactions (RegiSCAR) study group published a scoring system in 2007 to assess potential cases of DRESS syndrome (4). The criteria for RegiSCAR included the following: fever (>38.5°C), lymphadenopathy, eosinophilia, atypical lymphocytosis, skin

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involvement, visceral organ involvement, resolution (>15 days), and exclusion of other potential causes (e.g., antinuclear antibody, blood cultures, serology for hepatitis A virus, hepatitis B virus, hepatitis C virus, chlamydia, and mycoplasma). To meet the definitive diagnosis of DRESS syndrome, the final RegiSCAR score must be ≥5 (4).

Levetiracetam is a relatively new, nonaromatic, broad-spectrum antiepileptic agent that is considered effective and well-tolerated in the treatment of epilepsy. It was approved by the U.S. Food and Drug Administration as an antiepileptic drug in November 1999 (5). However, a few recent studies have reported cases of levetiracetam-induced DRESS syndrome (6–9).

We describe a case of DRESS syndrome presenting with the clinical manifestations of a virus infection during levetiracetam treatment for the control of seizures. When a patient presents to the emergency department with the clinical manifestations of a viral infection, emergency physicians should consider the possibility of drug hypersensitivity reactions in the differential diagnosis.

CASE REPORT

A 9-year-old girl was referred to our pediatric neurology department with a diagnosis of space occupying mass-related seizures. The patient was the sixth of 6 children of a nonconsanguineous couple, and all siblings were healthy. The history of the patient was unremarkable until 2 months before presentation. She was admitted to another state hospital about 2 months earlier because of seizures. The seizures occurred almost every day for a few seconds, starting from the right leg, and sometimes accompanied by contractions in the right corner of the mouth. Cranial magnetic resonance imaging scans revealed a space-occupying lesion with intense contrast uptake, measuring 9 × 6 mm in the left parietal vertex. The tumor was interpreted as a low grade neuroectodermal tumor. Levetiracetam therapy was started for the control of seizures.

The patient was admitted to our pediatric emergency department with skin rash and fever after 19 days of treatment. The patient had no significant medical history of any drug allergies. She was not receiving any other medications. Neither patient had traveled recently or had a history of blood transfusion. On admission, the patient was febrile to 39.5°C (103.1°F) with a heart rate of 108 beats/min, a respiratory rate of 28 breaths/min, blood pressure of 100/65 mm Hg, and oxygen saturation of 98%. The physical examination included the following: pruritic and erythematous maculopapular rash and exfoliative dermatitis covering the entire body surface, mild facial edema, pharyngitis accompanied by exudative membrane, bilateral cervical lymphadenopathy, and tender hepatomegaly 3 cm below the costal margin in the right midclavicular line. She did not have lesions in the conjunctiva, mucous membrane of the mouth, or genital area. With these findings, the patient was admitted to our pediatric neurology department with a diagnosis of epilepsy and a clinically suspected diagnosis of viral upper respiratory infection. Laboratory findings revealed leukocytosis (17.200/mm^3 [normal range, 4.500–13.500/mm^3]), lymphocytosis (9.200/mm^3 [normal range, 1.500–6.800/mm^3]), eosinophilia (2.900/mm^3 [normal range, <500 mm^3]), thrombocytopenia (104.000/mm^3 [normal range, 150.000–450.000 mm^3]), hepatitis (aspartate transaminase: 314 IU/L [normal range, 5–40 IU/L]; alanine transaminase: 224 IU/L [normal range, 5–40 IU/L]), and mild hyperbilirubinemia (total bilirubin, 2.9 mg/dL [normal range, 0.2–1.2 mg/dL]). On day 2, eosinophilia led to suspicion of having allergic reaction related to levetiracetam, and the antiepileptic therapy was ceased. Viral serology was demanded for the differential diagnosis of the drug-related rash and viral infection. The serologies of measles, rubella, Epstein–Barr virus, cytomegalovirus, varicella zoster, and parvovirus B19 were negative. On day 3, the patient was diagnosed with levetiracetam-associated DRESS syndrome. The patient had a score of 7 points according to the RegiSCAR scoring system; this was considered definitive for DRESS syndrome. With this diagnosis, intravenous steroid and antihistamine treatments were started in our pediatric neurology department. In addition, topical moisturizers were frequently used for skin hydration. Despite these treatments, the severity of her rash increased and she developed widespread skin edema on day 8. On examination, there was tachypnea (respiratory rate, 36 breaths/min), prolonged expiration, and crepitant rales. She had no history of chronic lung disease or autoimmune disorder. A chest radiograph revealed bilateral pulmonary interstitial infiltrates. Arterial blood gas analysis revealed hypoxemia (PaO_2, 74 mm Hg). Consequently, intravenous fluid replacement therapy and inhaled salbutamol were added to the existing treatment. The general condition of the patient was improved with this therapy. On day 11 postadmission, the patient had repeated seizures and topiramate treatment was started. On day 15 after admission, the patient was discharged with a significant improvement in laboratory results, fading of the skin rashes, and in good general condition (Figure 1). The clinical course of the patient is summarized in Figure 2. Oral prednisolone was continued with a dose of 1 mg/kg/day for 14 days, and then was slowly tapered and continued over 6 months. There was no repeat of seizures during the 6-month follow-up period with topiramate monotherapy.