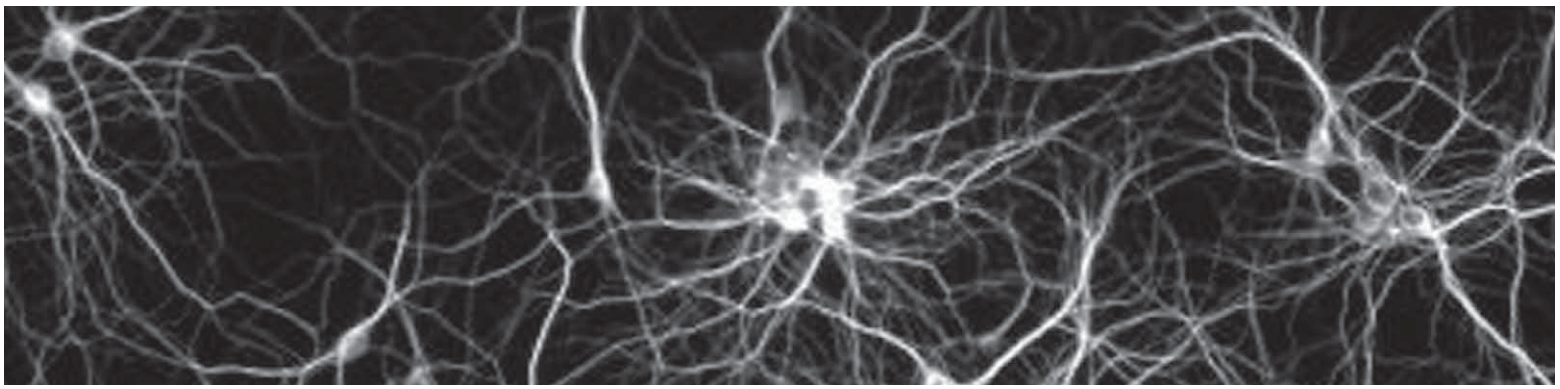

Carbamazepine-induced hypersensitivity reactions: case report

Borislav Vuković[1], Ivana Vuković[2], Dobrinka Petković[3], Andrea Šimić Klarić[4]

ABSTRACT – *Background:* Antiepileptic drugs can cause adverse cutaneous drug reactions. Most of the adverse cutaneous reactions have a favorable course, but there are serious cutaneous drug reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms. *Case report:* This paper presents a case of a 63-year-old male patient with ventriculoperitoneal shunt implanted six years before due to hydrocephalus, and treated at Department of Neurology in April 2014 for intracerebral hematoma in the left temporobasal region, which caused the first generalized tonic-clonic epileptic seizure. Carbamazepine was introduced in a daily oral dose of 400 mg. Five weeks after therapy initiation, he presented with generalized maculopapular exanthema and facial edema. Leukocytosis and monocytosis were verified on the second day of rash onset. He felt weakness on day 10 of rash onset, and high transaminase levels were recorded, increasing steadily for the next 10 days. Complete regression of rash occurred one month after carbamazepine discontinuation and corticosteroid therapy administration; his laboratory findings normalized after four months. *Conclusion:* Persistence of generalized maculopapular rash, facial edema, hematologic abnormalities, and toxic lesion of the liver suggest a hypersensitivity reaction to carbamazepine.

Key words: hypersensitivity reactions, carbamazepine, epilepsy

INTRODUCTION

Medications can cause adverse cutaneous reactions. According to research in the population of India, the major causative drug groups were antimicrobials, nonsteroidal anti-inflammatory drugs (NSAIDs) and antiepileptic drugs (1). Most of the adverse cutaneous reactions have a favorable course, but there are serious cutaneous drug reac-

[1] Požega General County Hospital, Department of Neurology, Požega, Croatia

[2] Rijeka University Hospital Center, Department of Pediatrics, Rijeka, Croatia

[3] Požega General County Hospital, Department of Infectious Diseases, Požega, Croatia

[4] Požega General County Hospital, Department of Pediatrics, Požega, Croatia

tions such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalized exanthematous pustulosis (AGEP) (2). The presence of an aromatic ring in antiepileptic structure is associated with a significantly increased risk of skin reactions. Skin reactions are three times more frequent with aromatic antiepileptic drugs than with nonaromatic antiepileptic drugs (3). Some antiepileptics such as carbamazepine, eslicarbazepine, phenytoin and lamotrigine can cause severe skin reactions, and carbamazepine causes most of them (3-6). Carbamazepine is an antiepileptic from the carboxamide group with marked anticonvulsive and psychotropic activity. Carbamazepine is presumed to inhibit voltage-gated sodium channels. Decreased release of glutamate and stabilization of neuron membrane is the basis of antiepileptic activity. Decreased dopaminergic and noradrenergic conduction of impulses affects manic manifestations. Due to the mentioned qualities, carbamazepine is used in the treatment of epilepsy, chronic painful syndromes and psychiatric disorders (bipolar affective disorder, resistant depression, borderline syndrome). Patients mostly tolerate therapy very well, but there are many side effects with a variable rate of occurrence, e.g., blood disorders, liver and kidney disorders, central disorders, and rash. Rare side effects are agranulocytosis, aplastic anemia, pseudolymphoma, systemic lupus erythematosus, SJS, TEN, DRESS, and toxic hepatitis. Carbamazepine shows interindividual and interethnic variability in clinical efficacy and adverse drug reactions (5,7,8). Carbamazepine can cause different forms of hypersensitive skin reactions in up to 10% of patients (7). DRESS is an infrequent but life-threatening reaction of hypersensitivity associated with antiepileptic drug intake, mostly carbamazepine and phenytoin. The clinical manifestations are rash, hematologic abnormalities, high body temperature, and affection of visceral organs, mostly liver (9). Symptoms typically occur 2-6 weeks after treatment initiation. High fever (usually >38 °C) and rash generally are the first signs, followed by other systemic symptoms including cervical, axillary and inguinal lymphadenopathy, acute liver and kidney failure, pulmonary and cardiac infiltrates, and hematologic abnormalities with eosinophilia and atypical lymphocytes (10). The incidence of DRESS in general population is 0.4/1,000,000 inhabitants (6). The incidence has been estimated to be between 1/1000 and 1/10,000 in the population exposed to anticonvulsants. The pathophysiology is unknown, combining immune and genetic factors (11).

The liver has numerous functions, including metabolism of many substances and medications. Medications can lead to hepatic impairment. Drug-induced hepatitis is found in 1%-3% of patients and 30% of all fulminant hepatitis cases are caused by medications. Drug-induced hepatitis can be successfully recovered, persist as a chronic disease, or lead to acute liver insufficiency and death (12).

CASE REPORT

We present a 63-year-old male patient with ventriculoperitoneal shunt implanted six years before due to hydrocephalus, probably of inflammatory etiology. In April 2014, he was treated at Department of Neurology for intracerebral hematoma in the left temporobasal region, with first generalized tonic-clonic epileptic seizure as its consequence. Carbamazepine was used for treatment in a daily dose of 400 mg. He also took the antihypertensive ramipril. During hospital stay, all laboratory findings where within the reference ranges. Neuroradiology diagnostics (multi-slice computed tomography (MSCT) of the brain) showed acute intracerebral hematoma of 22 mm in diameter, localized in the left temporobasal region, with surrounding edema, and enlargement of the third and lateral ventricles, which suggested compensated hydrocephalus with implanted catheter according to Pudentz. MSCT angiography of the head and neck vessels was normal. Electroencephalography (EEG) showed irritating dysrhythmic frontotemporoparietal changes, which tended to be better expressed over the left side, with paroxysmal tendencies. He presented with generalized itchy maculopapular exanthema and facial edema in the fifth week of carbamazepine therapy (Fig. 1).

We verified leukocytosis and monocytosis on the second day of rash appearance. The patient felt weakness on day 10 of rash onset, and we found a twofold increase of transaminase levels that increased steadily for the next 10 days, when the aspartate aminotransferase level was 10 times higher, alanine aminotransferase level 30 times higher, gamma-glutamyltransferase level 6 times higher and bilirubin level two times higher than normal; the level of alkaline phosphatase was also elevated. Carbamazepine therapy was discontinued immediately upon rash appearance and parenteral administration of methylprednisolone 1.5 mg/kg/day and antihistamine was introduced. We did not introduce a new antiepileptic drug, and the patient used only diazepam in the oral dose of 5 mg for a

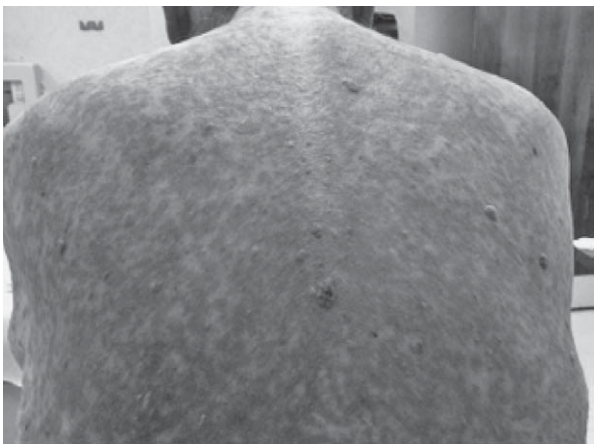

Fig. 1. *Generalized maculopapular exanthema.*

couple of days. No new epileptic seizures were observed. The rash was appearing daily throughout the next month. Complete rash regression was recorded at one month carbamazepine therapy discontinuation and corticosteroid therapy administration. Monocyte count was normal at two months and all laboratory findings were within the reference range at four months.

DISCUSSION

The skin is commonly affected within adverse reactions caused by medications. Most cutaneous reactions have a favorable course (2). Severe cutaneous adverse drug reactions such as SJS, TEN, DRESS and AGEP require fast diagnosis and therapy because lethal outcome is possible (4,5,9). Corticosteroids are administered in the treatment of skin reactions and systemic symptoms (3,6,9). Immunoglobulins or combination of corticosteroids, infliximab and high-dose intravenous immunoglobulins are used in the treatment of TEN (13). DRESS is an infrequent but acute and life-threatening reaction of hypersensitivity connected with taking antiepileptics, mostly carbamazepine and phenytoin. Clinical manifestations are rash, hematologic abnormalities, high body temperature, and affection of visceral organs, mostly liver (4,9). DRESS is an idiosyncratic reaction caused by medications, which appears at the beginning of therapy. Systemic corticosteroids are the current mainstay of treatment and they can reduce symptoms of delayed hypersensitivity reactions. A recommended starting dose is 1.0-1.5 mg/kg/day of prednisone or an equivalent drug. This dosage should be slowly tapered over 6-8 weeks to avoid a flare-up of symptoms (14). Disappearance of systemic manifestations is slow, over 1-6 months (6). Although there is still no universal consensus about the definition of DRESS, two diagnostic criteria are mainly adopted, the RegiSCAR study group (15), and the Japanese consensus group that emphasizes the existence of human herpes virus-6 reactivation (16).

Among antiepileptics, carbamazepine and phenytoin most often cause SJS/TEN and DRESS in Asian population. Liver is the organ most commonly affected with DRESS syndrome (5). In a study of cutaneous adverse drug reactions conducted in India from January 1995 till April 2013, lethal outcome for all skin changes caused by drugs was 1.71% and for SJS/TEN 16.39% (1). In Asian population, mortality for DRESS syndrome caused by antiepileptics was 7.7% and for SJS/TEN caused by antiepileptics 6.1%, while the most common outcome was liver lesion (5). Morimoto *et al.* describe a patient that presented with fatigue, high body temperature, cervical lymphadenopathy, generalized rash, face edema and perioral vesicles, leukocytosis and liver dysfunction during carbamazepine therapy for trigeminal neuralgia, with high antibodies of human herpes virus at the time of eruption (17). The incidence of skin changes as a reaction to medications in Indian population was 9.22/1000 patients. Maculopapular rash occurred in 32.39%, fixed drug eruption in 20.13%, urticaria in 17.49%, and SJS/TEN in 6.84% of patients. The most common cause of skin changes were antimicrobials (45.46%), nonsteroidal anti-inflammatory drugs (NSAIDs) (20.87%) and antiepileptics (14.57%). Commonly implicated drugs were sulfonamides (13.32%), beta lactams (8.96%), and carbamazepine (6.65%) (1).

Recent studies have revealed significant connection between human leukocyte antigens (HLA) and predisposition for adverse drug reaction as skin changes and liver lesion (7,8,18). Taking carbamazepine in persons with HLA-B* 15:02 is combined with the occurrence of SJS and TEN in South-East Asian patients only, whilst HLA-A*31:01 is associated with all phenotypes of hypersensitivity in multiple ethnicities (18). The HLA-B*15:02 allele has been shown to be strongly correlated with carbamazepine-induced SJS/TEN in South-East Asian population but not in European population. HLA-A*31:01 is associated with all phenotypes of hypersensitivity in multiple ethnicities (18,19). The presence of the HLA-A*31:01 allele was combined with carbamazepine-induced hypersensitivity reactions among persons originating from north Europe (19,20). The prevalence of HLA-A*31:01 allele in the population of north Europe is 2%-5%. The presence of HLA-A*31:01 al-

lele increases the risk of hypersensitive reaction by 5.0%-26.0%, whereas its absence reduces risk by 5.0%-l 3.8% (19).

Carbamazepine is the most frequently reported drug for DRESS syndrome among anticonvulsants, and liver is the most frequently affected organ (11). Hepatitis caused by medication can be successfully recovered, can persist as a chronic disease, or can lead to acute liver insufficiency and death. Diagnosis of medication-induced liver injury is based on history data on drug intake, clinical findings, laboratory results, and histopathologic diagnosis.

Our patient presented with generalized maculopapular rash, facial edema, leukocytosis, monocytosis, and toxic liver lesions five weeks after carbamazepine therapy initiation. Skin changes disappeared after one month of corticosteroid therapy, and laboratory findings normalized after four months. High body temperature and enlarged lymph nodes were not recorded in our patient.

CONCLUSION

Rash occurrence in patients taking antiepileptic drugs requires further follow up. In case of severe cutaneous drug reactions, it is necessary to stop antiepileptic therapy immediately and start with the administration of parenteral corticosteroid therapy. Systemic corticosteroids can reduce symptoms of delayed hypersensitivity reactions.

In our patient, persistence of generalized maculopapular rash, facial edema, hematologic abnormalities, and toxic lesion of the liver suggested a hypersensitivity reaction to carbamazepine.

Pharmacogenetic testing is recommended to detect patients at high risk of carbamazepine-induced hypersensitivity reactions.

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Address for correspondence: Borislav Vuković, MD, Požega General County Hospital, Department of Neurology, Osječka 107, HR-34000 Požega, Croatia; E-mail: vukovic.neuro@gmail.com

Karbamazepinom izvazvane reakcije preosjetljivosti: prikaz slučaja

SAŽETAK – *Uvod:* Antiepileptici mogu izazvati neželjene kožne reakcije. Većina kožnih promjena ima povoljan klinički tijek, međutim, postoje i teške kožne reakcije kao što su Stevens-Johnsonov sindrom, toksična epidermalna nekroliza, reakcija na lijekove s eozinofilijom i sistemskim simptomima. *Prikaz slučaja:* Prikazuje se slučaj 63-godišnjeg bolesnika kojemu je šest godina ranije postavljena ventrikuloperitonejska drenaža zbog hidrocefalusa, a u travnju 2014. godine je liječen na odjelu neurologije zbog intracerebralnog hematoma lijevo temporobazalno s posljedičnim prvim generaliziranim toničko-kloničkim epileptičkim napadajem. Uvedena je peroralna terapija karbamazepinom u dnevnoj dozi od 400 mg. U petom tjednu od primjene lijeka pojavio se generalizirani makulopapulozni osip praćen svrbežom i oteklinom lica, a drugog dana od pojave osipa zabilježena je leukocitoza i monocitoza. Desetog dana od nastanka osipa je uz osjećaj slabosti i malaksalosti zabilježeno povišenje vrijednosti transaminaza s porastom vrijednosti u sljedećih deset dana. Mjesec dana nakon ukidanja terapije karbamazepinom i nakon provedene kortikosteroidne terapije došlo je do potpune regresije osipa, a nakon četiri mjeseca uslijedila je potpuna normalizacija laboratorijskih nalaza. *Zaključak:* Pojava generaliziranog makulopapuloznog osipa, otoka lica, hematoloških abnormalnosti, toksične lezije jetre ukazuje na reakciju preosjetljivosti na karbamazepin.

Ključne riječi: reakcija preosjetljivosti, karbamazepin, epilepsija