

CASE REPORT

Patch testing is an effective method for the diagnosis of carbamazepine-induced drug reaction, eosinophilia and systemic symptoms (DRESS) syndrome in an 8-year-old girl

Ayşe Betül Büyüktiryaki,¹ Handan Bezirganoglu,² Umit Murat Sahiner,¹ Suleyman Tolga Yavuz,¹ Ayfer Tuncer,¹ Ates Kara³ and Cansin Sackesen¹

¹Pediatric Allergy and Asthma Unit, ²Department of Paediatrics, and ³Paediatric Infectious Diseases, School of Medicine, Hacettepe University, Ankara, Turkey

ABSTRACT

Drug reaction, eosinophilia and systemic symptoms (DRESS) is an acute and life-threatening disease, characterised by fever, rash and systemic symptoms, including lymphadenopathy, abnormal liver function, interstitial nephritis, pulmonary and cardiac infiltrates and haematological abnormalities with eosinophilia and atypical lymphocytes. The drugs mostly associated with DRESS are anticonvulsants, allopurinol, minocycline and sulfonamides. This syndrome is rarely seen in childhood even though a large number of children have anticonvulsant treatment. An 8-year-old girl was admitted with fever, lymphadenopathy and skin eruptions on her trunk. Her medical history was notable for epilepsy and carbamazepine treatment had been started 5 weeks previously. Laboratory studies showed a white cell count of 6200/μL (normal, 4100–11 200/μL) with 22% eosinophils and a γ-glutamyl transpeptidase level of 296 U/L (normal, 0–25 U/L). Laboratory tests for infections and collagen diseases were in the normal range. Persistence of fever and maculopapular eruption with generalised desquamation and the appearance of cheilitis and facial angioedema suggested a hypersensitivity reaction to carbamazepine. The carbamazepine was replaced with levetiracetam. All clinical symptoms improved within a week with corticosteroids and antihistamine treatment. Six

weeks after complete recovery an epicutaneous patch test with carbamazepine was performed and a carbamazepine-induced positive skin reaction was observed at 48-h. Carbamazepine-induced DRESS syndrome is a rare entity in children. An epicutaneous patch test is a useful tool for identifying the inducing agent for the DRESS syndrome and for identifying a safe anticonvulsant drug.

Key words: carbamazepine, DRESS syndrome, drug hypersensitivity, eosinophilia.

INTRODUCTION

Drug-induced hypersensitivity syndrome was first described in 1950 by Chaiken and colleagues¹ in a patient with fever, rash and hepatitis using an anticonvulsant drug. Since there is no consensus about the definition of this drug eruption, Bocquet and colleagues² proposed a new term drug rash with eosinophilia and systemic symptoms (DRESS). Subsequently, to attain a more appropriate term; the name ‘rash’ was changed to ‘reaction’ to include patients without eruptions. Multivisceral involvement differentiates DRESS from common drug-induced eruptions.

The incidence of the disease has been estimated to be between 1/1000 and 1/10 000 exposures to anticonvulsant drugs.³ The drugs mostly associated with DRESS syndrome

Correspondence: Dr Cansin Sackesen, Paediatric Allergy and Asthma Unit, School of Medicine, Hacettepe University, Ankara 06100, Turkey. Email: csackesen@yahoo.com

Ayşe Betül Büyüktiryaki, MD. Handan Bezirganoglu, MD. Umit M Sahiner, MD. Suleyman Tolga Yavuz, MD. Ayfer Tuncer, MD. Ates Kara, MD. Cansin Sackesen, MD.

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Abbreviations:

AGEP	acute generalised exanthematous pustulosis
DRESS	drug reaction with eosinophilia and systemic symptoms
FDE	fixed drug eruption
SJS	Stevens–Johnson
TEN	toxic epidermal necrolysis



Figure 1 Skin eruption on the neck.

are anticonvulsants (phenobarbital, phenytoin, carbamazepine and lamotrigine), antimicrobials (minocycline, β -lactams, sulfonamides, abacavir, nevirapine), allopurinol, dapson, sulfasalazine, neomercazole and fluindione.³ This acute and severe syndrome is characterised by the presence of fever, skin eruption and systemic symptoms including lymphadenopathy, abnormal liver function, interstitial nephritis, pulmonary and cardiac infiltrates and hematological abnormalities with eosinophilia and atypical lymphocytes.²

CASE REPORT

An 8-year-old girl was admitted to the emergency room with fever, lymphadenopathy and skin eruption on her trunk. She had been prescribed amoxicillin-clavulonate, paracetamol and hydroxyzine. Ten days later, she was re-admitted with continued fever, spreading eruptions all over the body and sore throat. Her medical history was notable for epilepsy that had been treated with carbamazepine for five weeks. She had disseminated maculopapular eruptions on her face, trunk and extremities along with generalised desquamation (Fig. 1,2), bilateral enlarged cervical lymphadenopathies and mild hepatosplenomegaly. Vancomycin, amikacin and sulbactam-ampicillin treatment had been started for an initial diagnosis of streptococcal infection. Laboratory studies showed a white blood cell count of 6200/ μ L (normal, 4300–10 300/ μ L) with 22% (normal, 0–5%) eosinophils, 41% neutrophils, 7% monocytes and 29% lymphocytes. Her C-reactive protein level was 7.5 mg/dL (normal, <0.8 mg/dL). Her alanine aminotransferase, aspartate aminotransferase and alkaline phosphatase levels were within normal ranges whereas the γ -glutamyl transpeptidase level was increased to 296 U/L (normal, 0–23 U/L). The serum levels of creatinine, blood urea nitrogen, immunoglobulin and complement levels (3 and 4) were in normal ranges, a urinalysis and chest radiography did not show a pathological result. Viral serology, anti-nuclear antibody, anti-double-stranded DNA, anti-streptolysin O, blood and throat cultures were negative (Table 1). Cervical ultrasound showed multiple lymphadenopathies on the cervical chain and abdominal ultrasound



Figure 2 Prominent desquamation on the antecubital fossa.

Table 1 Laboratory results of the patient

		Normal range
White blood cell count (/ μ L)	6 200	4 100–11 200
Lymphocyte (%)	29	18.8–50.8
Eosinophil (%)	22	0.8–5.0
Neutrophil (%)	41	40–75
Erythrocyte sedimentation rate (mm/h)	10	0–20
C-reactive protein (mg/dL)	0.5	0–0.8
Total immunoglobulin E (IU/L)	37	0–52
Alanine aminotransferase (U/L)	36	<39
Aspartate transaminase (U/L)	21	<51
Alkaline phosphatase (U/L)	120	<300
Gamma-glutamyl transferase (U/L)	296	0–23
Blood urea nitrogen (mg/dL)	12	5–18
Creatinine (mg/dL)	0.5	0.4–0.6
Complement 3 (mg/dL)	106	79–152
Complement 4 (mg/dL)	38	16–38
Anti-nuclear antibody	negative	negative
Rheumatoid factor (IU/mL)	<20	0–20

revealed mild hepatomegaly and splenomegaly. Echocardiography was normal. Bone-marrow aspiration showed 24% eosinophilia along with dysplastic changes. The persistence of fever and maculopapular eruption with desquamation, cheilitis and the appearance of facial angioedema that were unresponsive to antibiotic treatment during the follow up suggested a hypersensitivity reaction to carbamazepine. A skin biopsy revealed acanthosis, parakeratosis and spongiosis in the epidermis, perivascular oedema and mononuclear cell infiltration including eosinophils in the dermis. By fulfilling the proposed criteria of Bocquet and colleagues² and also the RegiSCAR study group,⁴ she was diagnosed as having DRESS syndrome. Consequently, all antibiotics were stopped and carbamazepine was replaced with another anticonvulsant drug, levetiracetam. Her symptoms resolved rapidly after withdrawal of carbamazepine and a short-term treatment including systemic corticosteroids and antihistamine. Her pathological laboratory findings returned to normal ranges within 4 weeks.

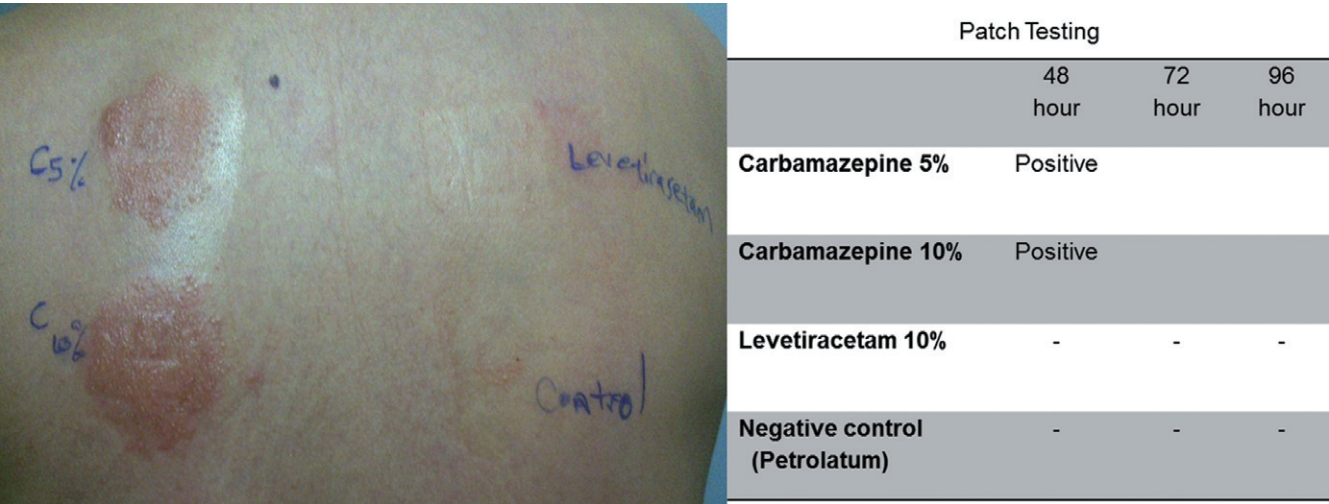


Figure 3 Patch test with carbamazepine 5 and 10% dilution, levetiracetam and control.

In order to identify the inducing agent of the hypersensitivity reaction for this patient an epicutaneous patch test with carbamazepine was performed 6 weeks after her complete recovery. Carbamazepine was diluted in petrolatum at a 5% and 10% concentration and the levetiracetam was diluted to a 10% concentration.⁵ Petrolatum alone was used as a negative control. Patch tests were applied on the upper back using IQ square chambers (Chemotechnique, Vellinge, Sweden). All reactions were negative after a 20 min reading. The patch tests with all concentrations of carbamazepine in petrolatum induced a strongly positive skin reaction in 48 h; levetiracetam and the negative control did not induce a delayed type hypersensitivity reaction (Fig. 3). The convulsions of the patient were under control after the levetiracetam treatment without inducing a delayed type hypersensitivity reaction.

DISCUSSION

DRESS syndrome is an acute, severe and life-threatening disease with a mortality rate of about 10%, which is frequently associated with systemic organ involvement, involving liver dysfunction, renal impairment and interstitial pneumonitis.⁵ Myocarditis, thyroiditis, encephalitis and type 1 diabetes mellitus have also been reported as manifestations of this syndrome. DRESS syndrome is more common in adults and rarely seen in children. The symptoms generally begin 2–6 weeks after beginning treatment, and fever and cutaneous eruptions are the most common features. Facial oedema is a typical finding for DRESS syndrome and prominent eosinophilia is the most common haematological abnormality, affecting 40% of patients.⁶ The liver is the organ most often involved and the degree of liver involvement ranges from mild elevation in transaminase levels to fulminant hepatic necrosis. The isolated elevation of γ -glutamyl transpeptidase levels without acute liver disease may exist, as seen in our patient.³ It has been suggested that a defect in detoxification mechanisms

induces the accumulation of the toxic metabolites of carbamazepine and may lead to cell death or initiate immune responses involved in DRESS syndrome.⁵

Aromatic anticonvulsant drugs are the most common causative drugs (carbamazepine, phenytoin and phenobarbital) and carbamazepine is the most frequently reported drug for DRESS syndrome among anticonvulsants.⁵ The cross-reactivity rate between aromatic anticonvulsants has been reported as 80% and an alternative drug from another group of anticonvulsants should be selected.⁷ Hence, in our patient carbamazepine treatment was replaced with levetiracetam and at the time of writing she has been seizure-free for 4 months.

Differential diagnosis includes Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), hyper-eosinophilic syndrome and Kawasaki disease. Infectious diseases in particular can mimic the syndrome in children and appropriate laboratory tests must be done to make the differential diagnosis. Because of this diversity in clinical presentations, the RegiSCAR study group⁴ and Shiohara and colleagues⁸ reported new diagnostic criteria for DRESS cases that emphasises the existence of human herpes virus-6 reactivation.

A validated, gold standard test for diagnosis of DRESS syndrome is not yet available, but drug provocation tests must be avoided because of the risk of a life-threatening reaction. Both patch and intradermal tests are suggested as useful diagnostic tools in non-immediate drug hypersensitivities. Although the sensitivity of patch tests is lower than intradermal tests, they can be performed with commercial drugs and their safety is higher than intradermal tests. Therefore, in severe drug hypersensitivities (e.g., TEN, SJS, DRESS, severe bullous exanthemas) patch tests are recommended as the first line of investigation after a risk/benefit analysis.

Since immune suppression in the acute phase may decrease skin reactivity, while excited skin may cause a

false positive result, the optimum time for performing a patch test should be at least 6 weeks after the resolution of the symptoms. Petrolatum is the most commonly used vehicle for dilution and with regard to the preferred vehicle, false positive results may be seen; therefore the type of drug must be taken into account in the determination of vehicle utilised.

The allergen is usually applied on the back of the patient on unaffected, untreated and uncleaned skin under chambers fixed with a hypoallergenic tape. The readings are done at 48 and 72 h following the application according to International Contact Dermatitis Research Group criteria.⁹ In some cases, positive results might occur 96 h or later. Although drug concentrations can vary between 0.0001 and 100% pure material, most preferred concentrations range from 1 to 10%. In order to prevent any relapse, concentrations up to 10% are recommended, either with the pure substance or a commercial form of the drug.¹⁰

Either the clinical features of the adverse drug reaction or the type of drug tested influence the success of patch testing. Therefore, several attempts have been made to evaluate the value of patch testing. The results of the study by Wolkenstein and colleagues¹¹ assessing patients with severe drug reactions, such as SJS and TEN or acute generalised exanthematous pustulosis (AGEP) revealed that the sensitivity of patch tests in SJS and TEN is weak and patch testing is inappropriate in these diseases. In fixed drug eruption (FDE), more positive patch test results are observed on the residual pigmented skin site of drug reactions rather than unaffected skin of the back.¹² As a result, patch testing has been found to be valuable in investigating maculopapular rash, eczema at drug injection sites, photosensitivity, FDE, AGEP and symmetrical drug-related intertriginous flexural exanthema along with DRESS; however it is less useful in SJS and TEN.^{15–16}

As mentioned above, results of patch testing also depend on the type of culprit drug, and the positive predictive value of the tests are reported to be between 20–80%;⁵ however negative results do not exclude the possibility of drug hypersensitivity. Recent studies have obtained more favourable patch testing results with anticonvulsant drugs, especially with carbamazepine. In a previously cited study of Santiago and colleagues,¹⁷ 13 of 18 (72.2%) suspected cases of carbamazepine-induced DRESS syndrome had a positive patch test, whereas in cases where the culprit drug was phenytoin or allopurinol, the positive patch test rate was as low as 14.3 and 0%, respectively. In another study by Galindo and colleagues,¹⁸ better results with carbamazepine (positive predictive value [PPV] 75%) and phenytoin (PPV 60%) were reported along with very low positive test results with phenobarbital (PPV 25%) and lamotrigine (PPV 25%).

In conclusion, even though delayed hypersensitivity reactions are rare in childhood, we present here an 8-year-old girl with carbamazepine-induced DRESS syndrome. Patch

testing is a useful tool for identifying the inducing agent of DRESS syndrome and for determining a safe anticonvulsant drug.

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