Neurología 40 (2025) 406—408

NEUROLOGÍA

www.elsevier.es/neurologia

LETTER TO THE EDITOR

DRESS syndrome and flare-up due to antiepileptics: how to solve the problem

Síndrome de DRESS y reactivación cruzada por otros antiepilépticos: cómo resolver el problema

Dear Editor,

One of the most severe drug hypersensitivity reactions is drug rash with eosinophilia and systemic symptoms (DRESS) syndrome. It typically presents with extensive rash, fever, adenopathies, and peripheral eosinophilia, and may affect internal organs such as the liver or kidneys. The most frequently involved drugs are antibiotics, other anti-infective agents, and antiepileptic drugs, and less frequently other types of drugs. Among antiepileptic drugs, those that most frequently trigger DRESS syndrome are drugs with an aromatic ring structure, including carbamazepine, oxcarbazepine, phenytoin, phenobarbital, and lamotrigine, and less frequently such others as valproic acid, ethosuximide, levetiracetam, and zonisamide.[1—4] In patients with DRESS syndrome, switching from the drug causing the syndrome to another may cause symptom reactivation. This second hypersensitivity reaction is known as cross-reactivity phenomenon or flare-up, and has been described with antibiotics, paracetamol, and antiviral drugs but not with antiepileptic drugs. Diagnosis of this phenomenon is vital, as the second drug may subsequently be tolerated.[5] Identifying the drug involved in DRESS syndrome is crucial, as the mortality rate may be as high as 20%.[6]

We report the case of a 35-year-old man with history of untreated familial multiple cerebral cavernomatosis that manifested with epileptic seizures. Treatment was started with phenytoin, with successive introduction of valproate and levetiracetam due to lack of response; seizure control was achieved with the combination of all 3 drugs. Ten days later, the patient presented fever of 39 °C, seizures, progressive maculopapular rash affecting more than 50% of the body surface area, and oedema in the eye and hands. A blood count revealed eosinophilia (0.82×10^9 cells/L), with the biochemistry profile showing increased liver enzyme levels (gamma-glutamyl transferase [GGT] of 807 U/L, glutamic-oxaloacetic transaminase [GOT] of 294 U/L, and glutamate pyruvate transaminase [GPT] of 460 U/L). Kidney function was normal. Treatment was discontinued and the patient improved in the following 3 days. Levetiracetam was reintroduced and rash worsened at 3 days, and fever of 39 °C was observed. The blood analysis showed leukocyte count of 21.99×10 cells/μL, eosinophilia (2.43×10^9 cells/L), GGT of 952 U/L, GOT of 222 U/L, GPT of 344 U/L, total bilirubin of 3.44 mg/dL, and direct bilirubin of 3 mg/dL, with normal kidney function. Levetiracetam was discontinued and corticosteroid treatment was started (oral prednisone at 30 mg/12 h); the patient's condition progressed favourably with no fever. Five days later, treatment was started with zonisamide, and the patient's general status worsened, rash spread, and fever of 39 °C and facial oedema manifested after 48 hours. The biochemistry profile showed increased levels of GGT (693 U/L), GOT (1425 U/L), and GPT (1479 U/L). All drugs were discontinued and symptoms resolved in 2 weeks, with normalisation of blood analytical parameters (Fig. 1).

No active infection was observed in the serology tests for hepatitis A, B, and C; Epstein—Barr virus; cytomegalovirus; or herpes simplex virus.

At 8 weeks, epicutaneous patch testing (PT) was performed with phenytoin, levetiracetam, and valproate (pure, and diluted at 1%, 10%, and 20% in water) as well as zonisamide (pure, and diluted at 1%, 10%, and 20% in Vaseline), with positive results at 48-96 hours for pure and 20% diluted phenytoin; negative results were obtained for the remaining drugs.

We subsequently followed the procedure described by Beeler et al.[7]: a lymphocyte transformation test (LTT) was performed to measure CD69 expression in CD4+ T cells using flow cytometry when the patient is exposed to the drug; the test yielded positive results for phenytoin and negative for valproate, zonisamide, and levetiracetam.

PT and LTT have been shown to be useful in diagnosing late lymphocyte-mediated drug reactions.[7,8] Both methods yielded positive results for phenytoin only; using the RegiSCAR (registry of severe cutaneous adverse reactions) scoring system to assess DRESS syndrome, we obtained a score of 4. Therefore, the patient was diagnosed at that time with

DOI of refers to article:
https://doi.org/10.1016/j.nrl.2023.11.006.

https://doi.org/10.1016/j.nrleng.2025.04.004

Figure 1 Progression of blood analytical parameters from onset of phenytoin treatment. GGT: gamma-glutamyl transferase; GOT: glutamic-oxaloacetic transaminase; GPT: glutamate pyruvate transaminase.

probable phenytoin-induced DRESS syndrome.[1,6] Although the drug provocation test is the gold standard for the diagnosis of hypersensitivity to drugs, it is contraindicated in the DRESS syndrome because it may cause injury to internal organs.[9] Based on the LTT and PT results and the need for treatment with antiepileptic drugs, a drug provocation test was performed with levetiracetam, zonisamide, and valproate (25% of the total dose was first used; after subsequent monitoring of the patient for 60 minutes, the rest of the dose was administered). No reaction was observed. The definitive diagnosis was phenytoin-induced DRESS syndrome with a flare-up following levetiracetam, zonisamide, and valproate administration.

This reaction may be explained according to the p-i concept (pharmacological interaction of drugs with immune receptors): immune stimulation during hypersensitivity to the drug may, similarly to generalised viral infections, lower the reactivity threshold of T cells to drugs and therefore lead to the rapid onset of symptoms of hypersensitivity to the newly administered drug, which may subsequently be administered in the absence of cofactors.[10]

From the time of symptom resolution, it took 2 months to diagnose phenytoin-induced DRESS syndrome and the patient received no antiepileptic drug. The patient has remained asymptomatic under treatment with levetiracetam at 500 mg/12 h.

LTT and PT may be useful for diagnosing phenytoin-induced DRESS syndrome and flare-up reactions following levetiracetam, zonisamide, and valproate administration.

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9 May 2023