

# Drug-Induced Hypersensitivity Syndrome (DRESS) by Phenobarbital - Case Report and Literature Review

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## Abstract

Drug-induced hypersensitivity syndrome (DHS), also named drug rash with Eosinophilia and systemic symptoms (DRESS) is a potentially dangerous side effect of some drugs, especially antiepileptic drugs (AEDs) such as phenobarbital, phenytoin, carbamazepine, lamotrigine, primidone, etc. It can also be caused by other drugs, such as sulfonamides and captopril. Diagnosis of DHS may be difficult because of the variety of clinical and laboratory abnormalities and manifestations and because the syndrome may mimic infectious or collagen vascular disorders. Management includes immediate withdrawal of the culprit drug, supportive care and systemic steroids or Immunoglobulins (IVIG). Here, we briefly reviewed the literature, followed by a case report that had all of the criteria of DRESS without eosinophilia.

**Keywords:** Phenobarbital, Drug Hypersensitivity Syndrome, Child, Case Report

## 1. Introduction

Drug rash with Eosinophilia and systemic symptoms (DRESS) syndrome is a rare and severe drug reaction that is induced by many drugs such as aromatic anti-convulsants, sulfonamides, captopril, non-steroidal anti-inflammatory drugs and some antimicrobials. However, this term (DRESS) may be a medical misnomer, because eosinophilia is not a constant laboratory finding, thus, skin and systemic involvement are variable. Pathophysiologically, drug-induced hypersensitivity syndrome (DHS) is an immune-mediated reaction involving macrophage and T-lymphocyte activation and cytokine release, although no consensus has been reached as to its etiology (1). Incidence of this syndrome ranges from 1 in 1,000 to 1 in 10,000 drug exposures and children are less affected than adults (2). The DRESS syndrome presents a diffuse cutaneous rash, fever, hematologic abnormalities (eosinophilia, leucopenia or atypical lymphocytosis), and some organ involvement (hepatitis, nephritis, and carditis) usually two to eight weeks after the initiation of drug therapy, with a possibility of persistence or even worsening of symptoms despite the discontinuation of drug (3). Drug-induced hypersensitivity syndrome can mimic severe sepsis, viral infection, adult-onset Still's disease, or lymphoproliferative malignancies (3). Phenobarbital has traditionally been used in the management of epilepsy (4). This drug is barbituric acid, with a molecular weight of 232.23 (5). Phenobarbital such as some antiepileptic drugs, can cause unpredictable

(idiosyncratic) hypersensitivity reactions that involve the skin and other internal organs (liver, kidneys and heart); however, involvement of the hematologic system is very unusual (6). Generally, drug induced hypersensitivity syndrome (DHS) includes a triad of symptoms that consists of dermatologic reactions, fever and evidence of systemic organ involvement (7). Phenobarbital can cause more severe and potentially dangerous adverse reactions such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) (8). Usually, we expect severe liver involvement to appear in SJS/TEN. On the other hand, neutropenia was almost always seen in other aromatic antiepileptic drugs, especially carbamazepine (9). Therefore, existence of severe hepatitis and marked neutropenia without eosinophilia in our case was rare and interesting.

## 2. Case Presentation

An 18-month-old male infant was admitted with fever and skin rashes to our neurologic ward. He was a known case of congenital hypothyroidism. He had received Phenobarbital during the last nine days (5 mg/kg/d) due to a second attack of complex febrile seizure. His motor developmental milestones were appropriate for his age but his speech delay was obvious. There was no history of intoxication and other drug consumption except daily levothyroxine since 15 months ago. He was not septic and there was no evidence of other similar conditions such as eruptive viral

disorders. Physical examination revealed diffuse erythematous, macular rash without mucosal involvement and skin detachment (Figure 1). He had a 38.5°C fever (axillary). His neurologic examination was unremarkable. He had no hepatomegaly. His abdominal ultrasound was normal. Our patient was not toxic but was ill and irritable. His general physical exam was unremarkable. His laboratory data on admission was as follows: white blood count (WBC) = 2,100 mm<sup>3</sup> (Neut: 35%, Lymph: 63%, Eos: 2%), normal biochemistry panel, urinalysis, negative blood and urine cultures. His Phenobarbital discontinued as soon as possible, and hydroxyzine with acetaminophen was begun for him. After 48 hours, we performed a complete blood count (CBC) and liver function test (LFT) for this infant because of continuation of his fever: WBC = 2400 mm<sup>3</sup> (Neut : 25%, Lymph: 69%, Eos: 3%, Mono: 3%), Aspartate Amino Transferase (AST): 355 u/L (normal range : up to 30 u/L), Alanine Transaminase (ALT): 390 u/L (normal range : up to 30 u/L), alkaline phosphatase: 750 u/L (normal range : up to 500 u/L for infants), Bilirubin (total): 1 mg/dL. Our patient was observed and his general condition was better after four days from admission and he was afebrile. Despite neutropenia and hepatic involvement, we didn't use corticosteroid for him. The patient's 5th day lab data were as follows: WBC = 4200 mm<sup>3</sup> (Neut: 40%, Lymph: 59%, Eos: 1%), AST: 245 u/L, ALT: 280 u/L. In the long run, our patient was discharged with a good general condition and mild skin rash without any drug except levothyroxine (for congenital hypothyroidism). His lab data one week after discharge: WBC = 5400 mm<sup>3</sup> (normal diff), AST: 55 u/L and ALT: 40 u/L.

He came back to our clinic after four weeks for follow up. His skin rashes had disappeared and his clinical condition was stable (Figure 2).

### 3. Discussion and Review of the Literature

Drug hypersensitivity syndrome (DHS) or drug rash with Eosinophilia and systemic symptoms (DRESS) is a serious complication of some drugs such as, antiepileptic drugs characterized by an extensive confluent rash, fever, lymphadenopathy, hematologic abnormalities, hepatitis, and involvement of the kidneys, lungs, heart, or pancreas that usually develop in the first two to eight weeks (10). It is increasingly apparent that there is a genetic predisposition to adverse drug reactions (11). Aromatic anticonvulsants (phenytoin, phenobarbital and carbamazepine) are the most common cause of DRESS. In the review of 172 cases reported as DRESS or DHS in the literature, carbamazepine remains the mostly reported (27% of cases) (12). Cross-sensitivity is as high as 75% among the aromatic anticonvulsants (13). There is a 10% mortality rate from DRESS, mostly due to liver damage thought to be secondary



**Figure 1.** Confluent Erythematous, Macular Rash on Face (With Informed Consent of his Parents)



**Figure 2.** Four Weeks After Discharge (With Informed Consent of his Parents)

to eosinophilic infiltration. The most important steps in managing patients with DRESS are recognizing the presence of this syndrome and immediately stopping the offending drug (13). Systemic corticosteroids have been considered the treatment of choice, especially in patients with internal organ involvement (14). The French society of dermatology published a report in 2010 outlining a consensus on therapeutic management of DRESS. They recommend the use of systemic corticosteroids at a dose equivalent to 1 mg/kg/day of prednisone in patients with any sign of severity including: liver transaminases greater than five times normal, renal involvement, or cardiac involvement. They further recommend the use of IVIG at a dose of 2 g/kg over five days for a patient with life-threatening signs such as renal failure or respiratory failure (15). As mentioned above, DHS or DRESS is potentially a very dangerous condition, especially in children. The hematologic abnormalities of DHS generally consist of eosinophilia, atypical lymphocytosis, lymphopenia and thrombocytopenia (16). In a descriptive study in Iran, Karimzadeh et al. evaluated 70 children with AEDs induced reactions, where 49 cases (70%) were due to phenobarbital and four children had DRESS with eosinophilia, leukocytosis and hepatic involvement (17). Our patient was an infant with severe liver involvement but without any hepatitis signs and/or symptoms. In other words, our case presented classic symptoms of DRESS without atypical lymphocytes and eosinophilia despite severe hepatic involvement. We managed this patient with anti-histamine drug (hydroxyzine). We did not use corticosteroid for hepatic involvement because eosinophilia was not found in this case and his general condition was good.

### 3.1. Conclusions

Mechanisms underlying DHS or DRESS syndrome remain poorly understood. Here, we report an interesting case with DRESS induced by phenobarbital with marked hepatic involvement and neutropenia without eosinophilia.

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