World Journal of Pharmaceutical Sciences
ISSN (Print): 2321-3310; ISSN (Online): 2321-3086
Published by Atom and Cell Publishers
Available online at: http://www.wjpsonline.org/
Review Article

Carbamazepine induced DRESS syndrome-Case report and brief review

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Received: 18-06-2015 / Revised: 16-07-2015 / Accepted: 25-07-2015

ABSTRACT

Drug Reaction with Eosinophilia and Systemic Symptom (DRESS) is a potentially life-threatening syndrome including severe eruption, fever, eosinophilia and internal organ involvement**.** A 17 year-old female with bipolar disorder was admitted with maculapapular rash accompanied by a fever and malaise. Patient shows signs of hepatocellular injury by elevated liver enzymes. Carbamazepine was immediately stopped, and the patient was treated by oral antihistamines and dermal corticosteroids.

Key Words: Dress syndrome, Carbamazepine, Adverse drug reaction

INTRODUCTION

Hypersensitivity syndrome is an idiosyncratic, serious drug reaction which is characterised by rash, fever, involvement of multiple visceral organs, and haematological abnormalities such as eosinophilia. Bocquet et al. have recently introduced the term drug rash with eosinophilia and systemic symptoms (DRESS) syndrome to better differentiation of drug hypersensitivity reaction from drug-induced pseudolymphoma [1]. The most commonly drugs causing hypersensitivity reaction includes antiepileptic drugs (mainly carbamazepine, phenytoin, phenobarbitol, lamotrigine), antibiotics (minocycline, b-lactams, sulfonamides), antiviral agents (abacavir, nevirapine), dapsone, sulfasalazine, and allopurinol [2-5].

Objective: We describe a case of carbamazepine induced dress syndrome with its pathogenesis and different approaches of management.

Case presentation: A 17 year-old female with bipolar disorder was admitted on 17 may 2014 to the Department of medicine for acute disseminated maculopapular rash accompanied by a fever of 38°C and malaise. She had a history of bipolar disorder for 1 month and had taken carbamazepine for 10days.After that she developed facial oedema and suffered from generalized pruritic erythematous patches with bullae formation and oozing, accompanied by fever and chills. Her family history was non-contributory. On physical examination, there was facial oedema with scales and diffuse generalized erythema with tense vesiculobullous lesions on the arms and legs Laboratory investigation shows minimal decrease in WBC and PLT counts (WBC 2.6 × 10^3/μL, PLT 121 × 10^3/μL), and mild with eosinophilia(eosinophils6%). blood coagulation parameters were normal (TT 19.1 s, INR 1.05). CPR and ESR were elevated (55.03 mg/L and 54 mm at 1 hour, respectively). Biochemistry revealed signs of hepatocellular injury manifested by progressive elevation of AST (up to 233 U/L), ALT (up to 512 U/L), GGT (up to 969 U/L) and ALP (up to 306 U/L), without signs of hepatomegaly, changes in liver sonographic structure or deposits in the gallbladder on abdominal ultrasound. Renal parameters were normal (urea 32 mg/dL, creatinine 0.79 mg/dL). Urinalysis revealed microscopic haematuria.

Carbamazepine was immediately stopped after drug induced hypersensitivity reaction and the patient was treated by oral antihistamines and dermal corticosteroids. We were informed to the pharmacovigilance centre about this case.

The patient's skin symptoms and laboratory abnormalities started improving on the tenth day of hospitalization. He returned at home after 2 weeks. One week after discharge, patient symptoms resolved. Her laboratory values returned to normal after one month.
The causal relationship between the drugs and adverse reactions was evaluated with the algorithm

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of Naranjo and WHO UMC scale which shows possible and probable respectively.

Discussion:

The acronym Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) was first used by Bocquet and colleagues in 1996 to describe patients exhibiting a drug-induced condition characterized by an extensive rash, fever, lymphadenopathy, hematologic abnormalities, hepatitis, and involvement of the kidneys, lungs, heart, or pancreas[1].The onset of symptoms is often delayed, occurring 2-6 weeks after drug initiation. The incidence of DRESS has been estimated to be between 1 in 1,000 and 1 in 10,000 drug exposures. It carries a mortality rate of 10-20%, with most fatalities the result of liver failure. Treatment consists of antihistamines, corticosteroids, and supportive therapy [6-8]. Severe cases of DRESS often require aggressive treatment; however, current pharmacologic treatment options are limited [9].

Pathogenesis

The pathogenesis of DRESS syndrome is not well understood. It is hypothesized as complex interaction between two or more of the following: 1. Accumulation of drug metabolites due to the genetic deficiency of detoxifying enzymes. The drug metabolites bind to cell macromolecules covalently causing cell death or inducing secondary immunological phenomena. Drug-specific T-cells activated and induces eosinophilic activation as well as activation of the inflammatory cascade by interleukin-5 release from [10].

2. Genetic associations between human leukocyte antigen (HLA) associations causes drug hypersensitivity syndrome. Human leukocyte antigen B (HLA-B*1502) is mainly associated with carbamazepine (CBZ)-induced Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) [11]; and HLA-B*1508 with allopurinol induced SJS/TEN [12]; and many others. It was also observed that the association of HLA-B*1502 and CBZ-induced SJS/TEN could be specifically related to ethnicity which is mostly observed in Chinese populations [13-16]. Furthermore [17-18], the association of CBZ-induced drug hypersensitivity reactions seems to be phenotype-specific.

3. The third hypothesis involved in the carbamazepine induced hypersensitivity reaction is virus-drug interaction. This phenomenon has been previously observed for herpes viruses (notably Epstein-Barr virus [EBV] [19]. As a result of an expansion of virus-specific and nonspecific T cells, the clinical manifestations seem to be appearing. In fact, drug-specific T-cells have been isolated from the blood and skin of patients in whom DRESS syndrome was induced by lamotrigine and carbamazepine [20-23]. Shiohara et al reviewed the latest evidence regarding the association of viral infections and drug rashes as well as the mechanisms of how viral infections can induce drug rashes. The clinical symptoms of drug hypersensitivity reactions observed due to the sequential reactivations of several herpes viruses (HHV-6, HHV-7, EBV, and cytomegalovirus) [23]. The same pattern of the herpes virus re-activation was observed in graft-versus-host disease (GVHD),Thus suggesting that DRESS may resemble GVHD in the sense that antiviral T-cells can cross-react with the drugs and do not only arise from the oligoclonal expansion of drug-specific T-cells [24-25]. Kano et al [29] also studied whether immunosuppressive conditions that allow HHV-6 reactivation could be specifically detected in the setting of anticonvulsant hypersensitivity syndrome (AHS). In order to test this idea, they performed serological tests for antibody titres for various viruses and found that serum immunoglobulin G (IgG) levels and circulating B-cell counts in patients with AHS were significantly decreased at onset compared with control groups ($P<0.001$ and$P=0.007$, respectively). These alterations returned to normal levels on the patient's recovery. Additionally, they observed that the reactivation of HHV-6 measured by a greater than fourfold increase in HHV-6 IgG titers was exclusively detected in patients with AHS who had decreased IgG levels and B-cell counts. These findings suggest an association between the severities of AHS and possibly DRESS syndrome.

The pathology behind our case study is not well understood. It might be due to the drug-specific T-cells activation and eosinophilic activation which leading to the activation of the inflammatory cascade by interleukin-5 release from. Our patient had no family history of dermatological reaction and drug allergy. Studies showed that female patients are more prone to get the ADR.

Treatment

The first step in the treatment of DRESS syndrome is to discontinue the causative drug. Patients with DRESS, although optimum treatment remains controversial, are usually treated with corticosteroid [26-27]. In individual cases, effective treatment was reported as with corticosteroids and intravenous immunoglobulin. However, no controlled trials of such therapies are present. Mean recovery time is 6.4 ± 9.4 weeks [27]. As different

from the regimes including conventional oral doses reported in previous studies, parenteral pulse corticosteroid therapy used is considered to be more successful because of both a more rapidly favourable clinical course and returning of liver tests to normal in shorter period. Treatments of methylprednisolone at a dose of 30mg/kg (max 1 g/day) and oral methylprednisolone at a dose of 1 mg/kg were successfully carried out in our case. As a result of treatment of oral methylprednisolone, healing process was seen to take shorter time, compared with those reported in the literature [27, 28].Consequently, healthcare professionals should be alerted to DRESS syndrome while evaluating skin rash, fever, systemic involvement and eosinophilia and, scarlet fever should also be kept in mind in the differential diagnosis. In such cases, prompt recognition and withdrawal of the causative drug are essential and first to be treated with methylprednisolone. It may be beneficial in the treatment of cases with DRESS syndrome, especially accompanied by internal organ involvement.

Systemic corticosteroids have been considered the treatment of choice, especially in patients with internal organ involvement. The French Society of Dermatology published a report in 2010 outlining a consensus on therapeutic management of DRESS [29]. 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 such as: transaminases greater than five times normal, renal involvement, pneumonia, hemophagocytosis, 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. In addition, they propose the use of steroids in combination with ganciclovir in patients with signs of severity and confirmation of a major viral reactivation of HHV-6 [29].

N-acetylcysteine (NAC) has been proposed as a potential therapy in drug detoxification. N-acetylcysteine has been used in high doses in case reports of DRESS syndrome due to anticonvulsants for clinical and biochemical improvement with side effect of development of angio-oedema of the face [30]. Further study and randomized controlled trials of these and other potential pharmacologic therapies will be important in establishing a standard of care and to improve understanding of how best to treat patients affected by DRESS syndrome.

SUMMARY

Although the mechanisms underlying DRESS syndrome remain poorly understood, there are a growing number of cases reported in children and adults that highlight the distinctive presentation of this hypersensitivity reaction. A diagnosis of DRESS syndrome should be considered in any patient with severe rash, fever, eosinophilia or lymphocytic changes. Prompt recognition, with supportive therapy and initiation of corticosteroids, may prevent or minimize additional organ system involvement.

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