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Drug Rash With Eosinophilia and Systemic Symptoms Syndrome in Infancy: A Report of Two Rare Cases

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Introduction: Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) syndrome is a severe form of adverse drug reaction which describes a potentially life threatening condition, associated with a high mortality rate. This syndrome is rarely seen in childhood even though a large number of children receive anticonvulsant treatment.
Case Presentation: We report here two infants under two months of age, whose findings were consistent with DRESS syndrome due to phenobarbital usage. Considering their age, these two cases appeared to be unique to our knowledge. Good responses were observed in both cases after stopping the culprit drug and administration of systemic corticosteroid.
Discussion: Early recognition of DRESS syndrome is of a particular importance. Although rare, in newborn infants with the presence of skin rash, liver involvement, hyper-eosinophilia and lymphadenopathy, DRESS diagnosis should be highly suspected and prompt intervention including withdrawal of causative drug is required to prevent potentially fatal outcomes.

Keywords: Drug Hypersensitivity; Phenobarbital; Eosinophilia

1. Introduction

DRESS (Drug Rash with Eosinophilia and Systemic Symptoms) is a term that has been used to describe a severe form of Hypersensitivity reaction. It reflects a potentially life threatening reaction to drugs which is associated with a high mortality rate. The occurrence of DRESS syndrome is rare, with, much fewer cases involving children compared to adults in the literature. Nonetheless, it is considered as a true pediatric dermatology emergency because of its potential threat to life (1-5).

A delayed onset of symptoms, 2 - 6 weeks after the initiation of drug therapy is a characteristic of DRESS syndrome (2-6). Various drugs such as phenobarbital, sulfasalazine, sulfonamides, carbamazepine, allopurinol, nevirapine and phenytoin have been reported so far to be the causes of DRESS syndrome (7-9). The clinical manifestations include a severe skin eruption, fever, lymphadenopathies, hematologic abnormalities (eosinophilia or atypical lymphocytes) and internal organs involvement (5). The most frequent type is liver involvement described by either the elevation of liver function tests or the presence of hepatomegaly. Cardiac or hepatic involvement may be the cause of death in fatal cases. The symptoms may persist or even aggravate despite the discontinuation of the culprit drug (2-6, 10).

DRESS has been initially described as the anticonvulsant hypersensitivity syndrome (11). This syndrome is rarely seen in childhood even though a large number of children receive anticonvulsant treatment (12). Here we report two unique cases of infants under two months of age, whose finding upshots were consistent with DRESS syndrome due to phenobarbital usage.

2. Case Presentation

2.1. Case One

The first case was a 1.5-month-old boy, admitted with diffiuse morbilliform rash mostly on distal parts of the limbs for one week. The patient had had a history of seizure three days after birth and had been receiving Phenobarbital tablet (15 mg) 1/2 twice a day due to an abnormal EEG since he was one month old. Mild hepatomegaly was detected on physical examination. Laboratory work up revealed eosinophilia, thrombocytopenia, mild increase in transaminase and alkaline phosphatase levels. On the suspicion of DRESS syndrome, phenobarbital was with-

Implication for health policy/practice/research/medical education:
This report highlights the DRESS (The Drug rash with eosinophilia and systemic symptoms) syndrome which is of special interest. The manuscript reports the emergence of this syndrome in early infancy.

held, and treatment with methylprednisolone was started for the patient (2 mg/kg/day) which was satisfactory. The patient's condition improved during the admission and symptoms including maculopapular rash disappeared over the next weeks.

2.2. Case Two

A 48-day-old girl was referred to our center with fever, maculopapular rash over the upper limbs and trunk, as well as diffused cutaneous petechiae for seven days. She had developed bilateral conjunctivitis. Leukocytosis, eosinophilia and thrombocytopenia were observed in the laboratory work up. The patient developed anemia during the course of admission. She was first diagnosed with idiopathic thrombocytopenic purpura (ITP) followed by suspicion of sepsis. Detailed medical history disclosed that the patient had been given phenobarbital prior to the symptoms for one week due to icter. Considering different findings made the previous impressions unlikely. A diagnosis of DRESS syndrome was suggested and treatment with methylprednisolone (2 mg/kg/day) was started for the patient. A good response was observed in the following 10 days.

3. Discussion

Drug-induced hypersensitivity syndrome is considered as a severe drug reaction characterized by fever, rash, and systemic involvement (3, 4, 13). Carbamazepine, phenytoin, phenobarbital, dapsone, mexiletine, salazosulfapyridine, allopurinol, and minocycline are among the drugs that may cause this syndrome. Cross-reactivity has been frequently reported among these drugs (14). It usually occurs 1 - 8 weeks after drug introduction which may potentially have fatal outcome. Antiepileptic hypersensitivity syndrome may have variable presentations such as cutaneous eruption associated with fever and lymphadenopathy, Stevens-Johnson syndrome, toxic epidermal necrolysis, and in the severe form, DRESS syndrome (15). The aromatic anticonvulsants (phenytoin, phenobarbital, carbamazepine) and sulphonamides are the most common causes of DRESS syndrome. The incidence is estimated to be one in 1000 to one in 10,000 drug exposures (5).

DRESS syndrome has no age or sex tendency; nevertheless, this syndrome is rarely seen in childhood even though a large number of children get anticonvulsant treatment (12, 16). In one review article, the mean age of patients diagnosed with DRESS syndrome was 40.7 and the average age of cases resulting in death was 49 years; however there were no differences for demographic and clinical variables between cases who died and those that resolved (5). We have formerly reported manifestation of DRESS syndrome in a five-year-old girl from our center (17). Similar manifestations have been reported in pediatric patients due to carbamazepine and phenobarbital (18, 19).

The two cases reported here showed the manifestations which seem to fulfill the clinical criteria of DRESS syndrome. They were two infants; a 1.5-month-old boy and a 48-day-old girl who developed similar presentation of diffuse morbilliform rash mostly on the distal parts. Other noteworthy findings were Mild hepatomegaly and fever in these cases respectively. Both of them had eosinophilia, thrombocytopenia and mild increase in transaminase and alkaline phosphatase levels on the laboratory work up. Following skin rash and systemic symptoms, hyper-eosinophilia is the third most frequently reported sign in the studies of DRESS. Liver is the most frequently involved organ whereas other organs such as kidney or central nervous system were rarely reported to be involved (5). Detection of DRESS syndrome is basically dependent on the exclusion of various diseases with similar manifestations that may be delayed in time (20). Although it rarely involves the pediatric population, it is considered to be a true pediatric emergency owing to its potential threat to life (4). Withdrawal of culprit drug and administration of systemic corticosteroid remain the mainstay of the treatment (18). On the suspicion of DRESS syndrome, phenobarbital was stopped and the patients underwent methylprednisolone treatment which resulted in good response.

Taken together, early recognition of DRESS syndrome is of a particular importance as the mortality rate may be up to 10%. In any patients with the presence of skin rash, liver involvement, hyper-eosinophilia and lymphadenopathy, DRESS diagnosis should be highly suspected and prompt intervention must be considered in order to prevent potentially fatal outcomes; though further studies are required to settle a consensus on the treatment guidelines.

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Authors' Contribution

First author and corresponding author contributed 100% and other authors 50%.

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