Brief Report

Autoimmune Diseases, End Organ Dysfunction and Adverse Drug Reaction Following Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): A Retrospective Cohort Study

Abstract

Context: Autoimmune diseases, organ dysfunction and new drug allergies are mentioned as long-term complications after DRESS. There is scarcity of data on this from the country. **Aims:** To determine the frequency of autoimmune diseases, organ dysfunction, and new drug allergies after the resolution of DRESS. **Settings and Design:** This retrospective cohort study was carried out among patients who received treatment for DRESS in a tertiary referral center. **Materials and Methods:** In this retrospective cohort study, DRESS patients who received inpatient care in the dermatology department of our tertiary referral center from August 2014 to February 2017 were included. We excluded patients aged 12 years or below and those who had not completed minimum two years after the resolution of DRESS as on December 2019. We collected information on new onset autoimmune disease, end organ damage and new drug allergies detected after the resolution of DRESS through a telephonic interview. Those who consented were evaluated in our department. **Results:** We could contact 40/50 (80%) identified individuals and all of them consented for telephonic interview. 17 patients gave consent for revaluation in our department. There were 22 females and 18 males. 17 had definite and 23 had probable DRESS. The frequency of detection of a new disease and a new drug allergy after DRESS was 10% (4/40) and 7.5% (3/40), respectively. We noted three (7.5%) autoimmune diseases (rheumatoid arthritis 1, alopecia areata 1, chronic autoimmune urticaria 1) and one end organ damage (chronic kidney disease) among the study participants. **Limitations:** Small sample size and retrospective study design were the limitations. **Conclusions:** Prospective studies with large sample size are needed to delineate the link between DRESS and autoimmunity, end organ damage, and new drug allergies.

Keywords: *Autoimmune disease, drug reaction, drug reaction with eosinophilia and systemic symptoms, end organ damage*

Sarita Sasidharanpillai, Amala Theresa Joseph, Kidangazhiathmana Ajithkumar[1], Keerankulangara Devi

Department of Dermatology and Venereology, Government Medical College, Kozhikode, [1]Department of Dermatology and Venereology, Government Medical College, Thrissur, Kerala, India

Introduction

There are a few cohort studies on autoimmune diseases and end organ damage in patients who recovered from DRESS and they suggest that DRESS can predispose to later development of these.[1-3] There is scarcity of information on the long term outcomes after recovery from DRESS owing to the difficulty in getting follow up details from patients during a symptom free period.

In this retrospective cohort of 40 cases, we tried to document the autoimmune diseases, organ dysfunction and new drug allergies detected after the resolution of DRESS.

Materials and Methods

We identified consecutive individuals (from the database of the prospective study on DRESS being carried out in our department) who received treatment for probable or definite DRESS (as per RegiSCAR DRESS validation scoring system) from August 2014 to February 2017. We excluded patients aged 12 years or below and those who have not completed minimum two years after the resolution of DRESS as on December 2019. Resolution of DRESS was defined as clearance of skin lesions, normalization of laboratory parameters and completion of treatment with systemic corticosteroids. We collected information on patient profile and the course of DRESS from the prospectively documented data.

We carried out a telephonic interview with the identified individuals (who were willing to participate in the study) with a pre-set

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Address for correspondence:
Dr. Sarita Sasidharanpillai, Associate Professor, Department of Dermatology and Venereology, Government Medical College, Kozhikode - 673 008, Kerala, India.
E-mail: saritasclt@gmail.com

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questionnaire. We enquired about the onset of any clearly diagnosed new diseases and end-organ dysfunction after the resolution of DRESS, or the onset of disease during the acute stage that has not resolved after DRESS.[1] We also collected information on new drug allergies detected after the resolution of DRESS. The time interval between the resolution of DRESS and the diagnosis of another disease/drug reaction was noted. All the participants were specifically enquired for any symptoms including loss of weight/weight gain, tiredness, increased sleep/insomnia, altered bowel habits, warm and moist hands, exertional dyspnoea, amenorrhea, hair loss, polyuria, polydipsia, polyphagia, photosensitive rash, pain and/or swelling of joints, oral ulcers, feeling of tightness of skin, symptoms suggestive of Raynaud's phenomenon, periorbital/pedal edema, tachycardia, and tachypnoea. They were encouraged to attend the outpatient clinic of our department for detailed evaluation.

We did a thorough clinical examination, complete hemogram, urine microscopy, random blood sugar estimation and renal, liver and thyroid function tests (T3, T4 and thyroid stimulating hormone) in all those who consented and visited our clinic. We did peripheral smear study, reticulocyte count and direct coomb's test in patients who had anemia (hemoglobin level <10 gm% in females and <12 gm% in males). We did skin biopsy (from a representative lesion), serology for anti-thyroperoxidase (antiTPO) antibody, antinuclear antibody, rheumatoid factor and anticyclic citrullinated peptide antibody, chest radiography and ultrasonogram of abdomen and pelvis wherever indicated (when patients had clinical or laboratory features of an autoimmune disease or organ dysfunction).

The study had the approval of the institutional ethics committee. Individual study participant gave verbal informed consent before the telephonic interview. Participants evaluated in the department gave written informed consent. The data were entered in Microsoft Excel and analyzed.

Results

From August 2014 to February 2017, 51 patients had received treatment for probable or definite DRESS in our department. One patient died during the acute stage of drug reaction. We collected details of the remaining 50 patients.

One patient died three years after DRESS due to myocardial infarction. We could contact 40 patients (80%). There were 22 females and 18 males. 17 had definite and 23 had probable DRESS. Age of the study participants ranged 23–70 years (mean 47.6 ± 11.8 years) at the time of recruitment to the study.

The time interval between the completion of the treatment for DRESS and the recruitment to the study ranged 33–64 months (mean 49 ± 9.3 months).

At the time of diagnosis of DRESS, four patients (4/40, 10%) already had a diagnosis of an autoimmune disease {Vitiligo (1), rheuhmatoid arthritis (1) and hypothyroidism (2)}.

Three study participants had developed an autoimmune disease (7.5%) after DRESS [Table 1]. The diseases were alopecia areata (1, 2.5%), rheumatoid arthritis (1, 2.5%) and chronic autoimmune urticaria (1, 2.5%). Their age at the time of DRESS was 52, 30, and 20 years respectively. The time interval between the resolution of DRESS and a definite diagnosis of the autoimmune disease was 50, 33, and 30 months, respectively (mean 37.7 months). The participant with chronic autoimmune urticaria had received the diagnosis from our department following a positive autologous serum skin test.

None of the study participants had received a diagnosis of new onset organ dysfunction in the period between the resolution of DRESS and the time of recruitment to the study.

In 37 out of the 40 participants (92.5%), DRESS was the first episode of drug allergy. One patient had a prior history of maculopapular rash to penicillin, while two others gave history of one episode each of adverse drug reaction prior to DRESS but were not able to provide more details.

There were a total six episodes of new drug allergies in three patients (3/40, 7.5%) after the resolution of DRESS. The interval between DRESS and the new drug reaction ranged 6–53 months (mean 30.3 months). One patient had new adverse reactions to multiple unrelated drugs and another one manifested allergic reaction to multiple drugs that were related to each other, but unrelated to the drug inducing DRESS. One patient who had received olanzepin for one month (without any adverse events) during the acute phase of DRESS, as a substitute for sodium valproate (for bipolar disorder) developed angioedema when the same was reintroduced three years later [Table 2].

All three patients who manifested new drug allergies and 4/37 (10.8%) who did not manifest any new drug reaction had disease flares during DRESS (*P* value 0.003).

23 study participants were not physically evaluated as they didn't have any subjective symptoms which they thought deserved a clinic visit. 17 individuals examined in our department did not show clinical features suggestive of an undiagnosed autoimmune disease warranting further evaluation.

One patient who had nephritis during DRESS showed elevated blood urea (72 mg%) and creatinine (2.8 mg%), when evaluated 40 months later, during the current study (No 3, Table 1). His renal parameters had returned to normal at the completion of treatment for DRESS. When contacted for telephonic interview, he consented for a detailed evaluation in department, though he did not suffer

Table 1: Autoimmune manifestations and end organ dysfunction after resolution of drug reaction with eosinophilia and systemic symptoms

Age	Gender	*Drug causing DRESS and indication for the drug	Interval between resolution of DRESS and recruitment to the study in months	Autoimmune manifestation		End organ damage (time interval between resolution of DRESS and diagnosis of disease)
				Manifestation of autoimmunity	Interval between DRESS and autoimmune manifestation in months	
56	M	Carbamazepine for Trigeminal neuralgia	53	Alopecia areata	50	-
33	F	Phenytoin for seizure prophylaxis	39	Rheumatoid arthritis	33	-
45	M	Phenytoin for seizure prophylaxis	40	Nil	-	Chronic kidney disease (40 months)
25	F	Antibiotic for cellulitis	60	Chronic autoimmune urticaria	30	-

DRESS: Drug reaction with eosinophilia and systemic symptoms

Table 2: New drug allergies after resolution of drug reaction with eosinophilia and systemic symptoms

Age	Gender	*Drug causing DRESS and the indication for the drug	Interval between resolution of DRESS and recruitment to the study in months	New drug hypersensitivity reaction	
				Interval between resolution of DRESS and the new drug reaction in months	Reaction pattern, offending drug, and indication for which drug was prescribed
44	F	Lithium for bipolar disease	54	6	DRESS, Cefadroxyl for urinary tract infection
				24	Maculopapular rash, Amoxycillin-clavulanic acid for dental infection
				53	Maculopapular rash, Amoxycillin after caesarean section
43	F	Sodium valproate for Bipolar disease	60	36	Exfoliative dermatitis, Venlafaxine for bipolar disease
				44	Angioedema, olanzapine for bipolar disease
55	F	Phenytoin for seizure prophylaxis	64	18	Interstitial nephritis, aceclofenac for knee joint pain

from any symptoms. The abnormality in renal function was an accidental finding and had remained undiagnosed in the intervening 40 months. He was normotensive, had normal glycemic status and a detailed evaluation by the nephrologist failed to identify a cause for the renal function abnormality. He is currently under follow up in the nephrology department for chronic kidney disease.

Discussion

Autoimmune diseases like type 1 diabetes mellitus, thyroid dysfunction, systemic lupus erythematosus, alopecia areata, vitiligo, autoimmune hemolytic anemia and sclerodermoid graft-versus-host disease, end organ dysfunction and new drug allergies are reported following the resolution of DRESS.[1-4]

We report 40 cases of DRESS evaluated after a minimum interval of two years after the resolution of the reaction (mean interval of 49 months). Pre-existing autoimmune diseases at the time of DRESS, observed in four study participants (10%) were similar to the previous reports.[2] This indicates the need to explore the possibility of DRESS itself being an expression of autoimmune diathesis.

The frequency of detection of a new disease after DRESS (4/40, 10%) was comparable to the observation of Chen *et al*. (6/52, 11.5%).[1] The interval between DRESS and the subsequent diagnosis of a new autoimmune disease (30-50 months) was comparable to one previous study (36-48 months) but longer than the same noted in another (during hospitalization for DRESS – 8 months).[1-3]

Alopecia areata and rheumatoid arthritis as observed in this cohort were reported following DRESS.[1,2] We did not come across any previous reports of chronic autoimmune urticaria following DRESS.

Previous authors found a higher frequency of autoimmune diseases among DRESS patients treated without systemic corticosteroids in comparison to those treated with the corticosteroid.[2,3] All the DRESS cases in this study had received prednisolone or equivalent, but autoimmune diseases were found in 7.5%. This was concordant to the findings of Chen *et al*.[1]

Chronic kidney disease following DRESS noted by us was concordant to literature.[1] Contrary to the previous observation that autoimmune diseases and end organ damage after DRESS were more frequent in younger persons and elderly respectively, we did not find any disparity in the age of those manifesting autoimmune disease (20, 30, and 52 years) or organ damage (42 years).[1]

Three individuals (3/34, 8.8%) developed new drug reactions after DRESS in the study by Ushigome *et al*. which was similar to our findings (3/40, 7.5%).[2]

A drug reaction itself, is proposed to serve as an indicator of lack of tolerance of one's immune system and a possible risk factor for allergic reactions to other drugs, as well as autoimmunity.[5]

One of our patients later developed hypersensitivity reaction on reintroduction of a drug that was introduced and tolerated during the acute phase of DRESS. Others have reported similar cases.[6,7] This probably suggests the need to restrict drugs to an essential minimum during the acute phase of DRESS.[6,7]

Same patient manifesting different types of hypersensitivity reactions to different drugs as observed by us [Table 2] was concordant to the findings of previous authors.[5,7]

Whether flare up reactions during the course of DRESS, is a risk factor for future allergy to unrelated drugs (as noted by us) needs evaluation.

The autoimmune diseases and the chronic kidney disease observed in this cohort are seen frequently in general population as well. The possibility of a chance occurrence of these diseases cannot be ruled out.

Limitations

Only 17/40 individuals (42.5%) could be physically evaluated. It is possible that we missed a few asymptomatic early diseases in those who were not physically evaluated. Further the study was not designed to assess development of autoantibodies following DRESS since we lacked information on the autoantibody profile of all the study participants before and during DRESS. Limited number of cases and the retrospective study design were the other limitations.

Autoimmune diseases, new drug allergies and organ damage observed after the resolution of DRESS in our cohort of 40 patients were 7.5%, 7.5%, and 2.5%, respectively. Comparative studies with a large sample size that prospectively follow up patients at regular intervals after resolution of DRESS and other drug reactions, may give an accurate information on the link between DRESS and autoimmunity, end organ damage, and new drug allergies.

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Conflicts of interest

There are no conflicts of interest.

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