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Research Article

CLINICAL STUDY OF DRUG REACTION WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS (DRESS) – WITH SPECIAL FOCUS ON THE INCITING DRUG AND THE INDICATION FOR STARTING THE DRUG

MERIYA ZACHARIA*, SEENA P, KIRAN SHAJ, NEIKHRIETSONUO KESIEZIE

Department of Dermatology Venereology and Leprosy, Government Medical College and Hospital, Kottayam, Kerala, India.
Email: drmeriyazacharia@gmail.com

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ABSTRACT

Objective: This study was undertaken to identify the most common drug causing drug reaction with eosinophilia and systemic symptoms (DRESS) in patients admitted in our center and possible factors associated with it.

Methods: This was a cross-sectional observational study of patients with DRESS admitted from January 2018 to December 2020. Data were entered in MS Excel and analyzed using SPSS software.

Results: Eighty-four consecutive patients who were diagnosed as DRESS were included in the study. The most common inciting drug was phenytoin and the most common indication for starting phenytoin was traumatic brain injury (TBI) to prevent seizures. DRESS to phenytoin after neurotrauma (NT) was more in patients who sustained combined extradural (EDH) and subdural hematoma (SDH), and those were managed conservatively for NT. None of the patients recognized fever as an initial feature of DRESS and did not stop the drug. More than one-third of patients with erythema multiforme (EM) like rash developed drug induced liver injury(DILI). The majority of patients who had sub-arachnoid hemorrhage (SAH) developed DILI.

Conclusion: Phenytoin though time-tested and cost-effective for prevention of seizures after TBI, it very commonly leads to DRESS which adds to the morbidity and rarely mortality of patient. In this present era of increasing road traffic accidents, using newer non-aromatic anticonvulsants may be more beneficial than phenytoin. The patients should be made aware of the likely time DRESS can occur, the earliest symptom of DRESS, and the need to stop the drug at the earliest.

Keywords: Drug reaction with eosinophilia and systemic symptoms, Phenytoin, Traumatic brain injury.

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INRODUCTION

Drug reaction with eosinophilia and systemic symptoms (DRESS) also called drug-induced hypersensitivity syndrome (DIHS) is an idiosyncratic multisystem disorder and is one of the severe cutaneous adverse drug reactions [1]. It is characterized by skin rash which may present as urticated, papular, exanthematous, morbilliform, erythroderma, erythema multiforme (EM) like eruption or pustules, and systemic involvement including hematologic and solid organ disturbances [1]. The most typical hematologic alteration is eosinophilia [2]. Pronounced lymphocytosis and presence of atypical lymphocytes may also be seen in DRESS [1]. Liver is the most frequently involved internal organ and it can range from mild transaminitis to fulminant hepatitis [1]. Abnormalities in renal, gastrointestinal, pulmonary, and cardiac organ systems can occur [3]. RegiSCAR study group developed a diagnostic validation score combining clinical and biologic criterion for validating the diagnosis of potential cases of DRESS as definite, probable, possible, or no case [4]. The common drugs causing DRESS are phenytoin, phenobarbitone, carbamazepine, allopurinol, anti-tubercular drugs, nevirapine, sulfonamides, furosemide, omeprazole, and ibuprofen [1]. Among the anticonvulsants, phenytoin is the most common offending drug [5].

The increasing number of road traffic accidents in the present day is leading to more number of head injuries. Phenytoin being cost-effective is routinely given to prevent seizures following acute TBI. This leads to increase number of DRESS to phenytoin. Hence, this study was undertaken to determine the various factors in these patients which can make them more prone for development of DRESS.

METHODS

This study was a cross-sectional observational study conducted in the Department of Dermatology, Government Medical College and Hospital Kottayam, Kerala from January 2018 to December 2020. Patients diagnosed as DRESS according to the RegiSCAR scoring system [1] and admitted in our dermatology ward were included in the study. All clinical and laboratory data were collected and entered in Microsoft Excel and analyzed using SPSS 22 software. Results are expressed in percentage and Mean±SD. Statistical analysis was done using Chi-square and Fischer extract and $p<0.05$ was considered statistically significant.

Inclusion criterion

All clinically definite cases of DRESS diagnosed by the RegiSCAR criterion were included in the study.

Exclusion criterion

Cases with incomplete data were excluded from the study.

RESULTS

A total of 84 consecutive patients with DRESS were taken up for the study. Out of this, 58 patients (69%) developed DRESS due to phenytoin and the rest 26 patients (31%) developed DRESS due to other drugs, as shown in Table 1.

Out of the 58 patients with DRESS due to phenytoin, 37 patients (63.8%) were given phenytoin after a traumatic brain injury, 35 patients had sustained a road traffic accident, and two patients had a fall from height.

In the rest 21 patients, phenytoin was started for different indication as shown in Table 2.

Age
The age of the patients with DRESS due to phenytoin after NT ranged from 17 years to 74 years. About 67.6% of patients were in age group 51–60 years. The mean age was 51.73±10.83 years.

Sex
About 73% patients were males and 27% were females among those with DRESS to phenytoin after neurotrauma.

Type of neurotrauma
The majority of patients (n=21, 56.8%) who developed DRESS to phenytoin had a combined EDH and SDH as shown in Fig. 1.

Surgical intervention done
In our study, 62.2% patients (n=23) with DRESS to phenytoin after neurotrauma were managed conservatively after their head injury whereas 37.8% (n=14) underwent surgical interventions for their neurotrauma.

Comorbidity
Diabetes mellitus was noted in 56.8% (n=21) of patients with DRESS to phenytoin after neurotrauma (Fig. 2).

Time interval between starting of drug and development of DRESS
We observed that 48.6% of patients with neurotrauma developed DRESS to phenytoin between 15 and 21 days after starting the drug. The median incubation period is 21 days. The earliest interval was 12 days and longest was 54 days.

Initial symptom
About 56.8% (n=21) had fever as the first symptom, 8 patients (21.6%) had fever and rash together, and 8 patients (21.6%) had rash alone as the initial symptom.

Discontinuation of drug at the onset of initial symptoms
None of the patients who had fever as the initial symptom stopped the drug as they had not recognized fever as a symptom of drug reaction. About 3 out of 8 patients (37.5%) had fever and rash and 5 out 8 patients (62.5%) of patients with rash alone as the initial symptom discontinued the drug. This difference was found to be significant with Chi-square value 14.87 and p value 0.001.

Type of rash in DRESS
About 54.1% (n=20) had urticated papules and plaques, 29.7% (n=11) had maculopapular exanthema, and 16.2% (n=6) had exfoliative dermatitis as part of DRESS.

Erythema multiforme (EM) like lesions
About 29.7% (n=11) had EM like lesions along with DRESS while 70.3% patients (n=26) did not have EM like lesions. About 11 out of 20 patients (55%) with urticated papules had EM like lesions. None of the patients with maculopapular rash or exfoliative dermatitis had EM like lesions. This difference was also found to be significant with Chi-square value of 13.30 and p value 0.001; however, sample size is low.

About 27 patients (73%) with DRESS due to phenytoin after neurotrauma had facial puffiness and edema of hands and feet.

About 9 patients (24.3%) had cheilitis as part of DRESS to phenytoin after neurotrauma.

Liver function test (LFT) derangement
All the 37 patients (100%) patients with DRESS due to phenytoin after neurotrauma had elevation of transaminases more than 3 times the normal value. None had elevated serum billirubin. In 24 patients (64.9%), transaminase levels progressively increased for more than 2 weeks in spite of stopping the culprit drug and starting steroids.

Renal function test (RFT) derangement
Only 1 patient (2.7%) had abnormal RFT but this patient already had chronic renal disease. No other patient with DRESS to phenytoin had altered renal function in our study.

EM like lesions and LFT
About 10 out of 11 patients (90.9%) with EM like lesions had persistent elevation of transaminase levels for more than 2 weeks. About 14 out of 26 patients (53.9%) without EM like lesions had persistent elevation

Table 1: Drugs implicated in DRESS

Drug	Number of patients	Percentage
Phenobarbitone	6	23.1
Carbamezipne	4	15.4
Sodium valproate	4	15.4
Sulfasalazine	4	15.4
Pantoprazole	3	11.5
Diclofenac	2	7.7
Itraconazole	1	3.8
Ceftriaxone	1	3.8
Dapsone	1	3.8

Table 2: Other indications for which phenytoin was started

Indications	Number of patients	Percentage
Intracranial space occupying lesion	8	38
Cerebrovascular accident	6	28.6
Seizure disorder	4	19
Hydrocephalus stenting	2	9.8
Aneurysm	1	4.8

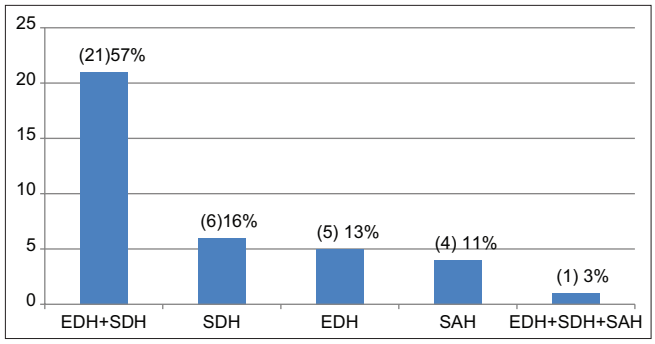

Fig. 1: Type of neurotrauma for which phenytoin was started

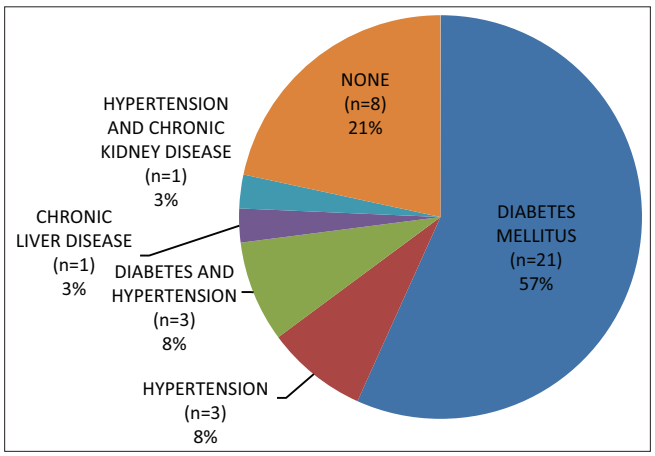

Fig. 2: Associated comorbidities in patients with DRESS due to phenytoin

of transaminase level for more than 2 weeks. This difference was significant with Chi-square 4.659 and p value of 0.031.

Drug-induced liver injury
About 10.8% (n=4) patients with DRESS to phenytoin after head injury progressed to develop drug-induced liver injury.

EM like lesions and drug-induced liver injury
About 36.4% patients with EM like lesions (4 out of 11 patients) progressed to develop drug-induced liver injury. Hence, all patients with DILI had EM like lesions. This difference is significant with Fischer exact value 0.005.

Subarachnoid hemorrhage and DILI
Four out of five patients with subarachnoid hemorrhage (80%) developed drug-induced liver injury as part of DRESS to phenytoin after head injury. None of the patients with other type of head injury progressed to DILI. This difference is significant with Chi-square 28.763 and p value 0.001.

DISCUSSION

Out of the 84 consecutive patients who were diagnosed as DRESS according to the RegiSCAR criterion [1], 69% developed DRESS after taking phenytoin. Among this, 63.8% of the patients were given phenytoin to prevent seizures after traumatic brain injury. In a study by Sasidharanpillai *et al*., in more than 50% cases of DRESS, the culprit drug was phenytoin [6]. In a study by Kardaun *et al*., antiepileptic drugs were implicated in 35% of DRESS and epilepsy was the most common indication [4]. In a study by Puneet *et al*., 70% developed DRESS due to anticonvulsant given after acute neurotrauma [5]. The high incidence of DRESS due to phenytoin in Indian studies may also point to a genetic factor in our population which accelerates the development of DRESS. HLA studies among the Indian population may be needed to conclusively state this. The mean age of the patients with DRESS due to phenytoin after neurotrauma was 51.73±10.83 years. In studies of DRESS conducted by Picard *et al*. and Sasidharanpillai *et al*., the mean age was 56 years and 37.3 years, respectively [6,7].

In our study, 73% of patients with DRESS to phenytoin after neurotrauma were males. This male preponderance may be due to the higher incidence of road traffic accidents among them. In studies by Sasidharanpillai *et al*. and Kardaun *et al*., there was a slight female preponderance in patients with DRESS [4,6].

In our study, 56.8% of patients who developed DRESS due to phenytoin after a neurotrauma had sustained a combined extradural and subdural hematoma. We also observed that 62.2% of our patients who developed DRESS were managed conservatively after neurotrauma. The validity of both these findings can be concluded only after more number of comparative studies.

In our study, 56.8% of patients with DRESS after neurotrauma had associated diabetes mellitus. In a study by Kardaun *et al*., 12% patients with DRESS in general had diabetes [4]. Further analytical studies are needed to conclusively state that diabetes is associated with increased risk of developing DRESS to phenytoin in neurotrauma patients.

We noted that 48.6% of the patients developed DRESS between 15 and 21 days after starting phenytoin. The median time interval was 21 days. In a study of DRESS in general by Kumari *et al*., the mean interval between intake of drug and onset of DRESS was 17–21 days [2]. In a study by Walsh *et al*., the mean interval was 27 days [8].

In 56.8% of our patients, fever was the first symptom, in 21.6% of patients, initial symptom was fever and rash together and 21.6% of patients had rash as the initial symptom. In a study by Sasidharanpillai *et al*., 57.7% of patients presented with fever and rash in DRESS in general [6]. None of the patients in our study who had fever as the first symptom stopped the drug at the onset of fever. However, among the patients who developed rash as the first symptom, 62.5% had stopped it and among the patients with fever and rash, 37.5% stopped the drug. The fact that fever can be the first symptom of a potentially serious drug reaction is often not recognized by the patients and they may not be aware of it.

The most common rash observed in our study was urticated papules and plaques which was seen in 54.1% of the patients. In a study by Walsh *et al*., on DRESS, 48% of the patients had urticated monomorphic papules [8]. In the study by Sasidharanpillai *et al*., on DRESS 76.9% of patients had a maculopapular rash [6].

In our study, 29.7% of patients with phenytoin-induced DRESS after a traumatic brain injury had erythema multiforme like lesions. In a study by Walsh *et al*., EM like lesions was found in 30% of patients with DRESS [8]. In our study, 55% of the patients with urticated plaques had EM like lesions while those with other type of rash as part of DRESS did not have EM like lesions. This was statistically significant.

In our study, 73% of patients with DRESS to phenytoin after neurotrauma had facial puffiness and edema of hands and feet. In a study by Kumari *et al*., 25% of patients with DRESS in general had facial puffiness [2]. In the study by Sasidharanpillai *et al*., facial edema was noted in 96.2% of patients with DRESS due to phenytoin [6].

Mild cheilitis was seen in 24.3% patients with DRESS after phenytoin intake following neurotrauma in our study. In the study by Kardaun *et al*., 56% of patients with DRESS in general had mild cheilitis while 42.4% of patients in the study by Sasidharanpillai *et al*. had mild cheilitis [4,6].

All the patients with DRESS to phenytoin after traumatic brain injury had more than 3 times elevation of transaminases than normal values and in 64.9% of the patients it progressively increased for more than 2 weeks. In a study by Sasidharanpillai *et al*., no liver involvement was noted in patients with DRESS due to phenytoin [6]. However, in a study by Picard *et al*., 97% of patients with DRESS in general had hepatitis [7].

We noted that 90.9% of patients with EM like lesions in our study had progressively increasing transaminase levels for more than 2 weeks in spite of starting systemic steroids. This was statistically significant. In the study by Walsh *et al*., EM like eruption with purpura and atypical targets was noted to have more severe hepatic involvement [8].

It was observed that 10.8% of patients with DRESS due to phenytoin after neurotrauma developed drug-induced liver injury. All these patients had EM like lesions. This was found to be statistically significant.

In our study, 80% of the patients with subarachnoid hemorrhage developed drug-induced liver injury as part of DRESS. This was also statistically significant.

There is a paucity of the literature in analyzing and comparing DRESS due to phenytoin specifically. Most studies have given insight into DRESS in general. More analytical studies are needed to compare the clinic-epidemiological aspects of DRESS due to phenytoin after neurotrauma and after giving it for other indications.

Phenytoin pharmacokinetics are altered in the presence of acute traumatic brain injury [9]. Protein binding of phenytoin is decreased in patients with head injury leading to an increase in free level of the drug [10]. After a severe head injury, several pharmacokinetic changes can occur in phenytoin metabolism such as blood-brain barrier disruption and changes in drug penetration, cytokine release which can affect cytochrome p450 enzyme system and alteration in protein binding [11]. The Vmax and Km values were significantly higher in head trauma patients than cerebrovascular accident patients [11]. Phenytoin is metabolized by CYP450 system to arene oxides metabolites which are normally detoxified by epoxide hydroxylase [12]. Head injury can act as an inducer of cytochrome p 450 system leading to increased formation

and accumulation of arene oxide metabolites [5]. This may explain the higher incidence of DRESS in head injury patients. Phenytoin remains the most widely used antiepileptic in post-traumatic seizure prophylaxis due to cost efficacy. Phenytoin is started based on ideal body weight in ICU rather than actual body weight which is difficult to obtain [13].

Our observation highlights that DRESS due to phenytoin after neurotrauma was more common in the sixth decade and in those patients after a combined EDH and SDH. It was also more in neurotrauma patients who were diabetic. The majority of patients with SAH developed drug-induced liver injury. The incubation period was slightly shorter than that classically described for DRESS in general. Furthermore, our study highlights that patients with urticated papules and plaques as part of their skin lesions of DRESS are more likely to have EM like lesions. All the patients had significantly elevated transaminase levels but our study highlights that the majority of the patients with EM like lesions had progressively increasing liver enzymes levels. Furthermore, in our study, all the patients who developed DILI had EM like lesions. Whether the type of neurotrauma, the surgical intervention, associated comorbidities, alters the internal milieu of the brain and CSF and accelerates that the development of DRESS needs to be validated by further analytical studies.

Limitations of the study

1. Small sample size.
2. Our study was an observational study; hence, the findings need to be validated with further analytical studies.

CONCLUSION

Phenytoin started after traumatic brain injury to prevent seizures was the most common cause of DRESS in our study. Maximum number of patients who developed it had combined EDH and SDH and were treated conservatively after neurotrauma. The majority of patients who progressed to DILI had sustained SAH. It has already been reported that phenytoin metabolism gets altered after traumatic brain injury. Development of DRESS adds to the morbidity in these patients. Further analytical studies are needed to find the various factors that can lead to DRESS in patients taking phenytoin after a head injury. With the advent of newer non-aromatic anticonvulsants, it is better to start on these newer drugs than phenytoin to prevent seizures after head injury. It is also imperative that patient and the bystander be made aware about the earliest symptoms of DRESS so that the drug can be stopped at the earliest.

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WORK ATTRIBUTED TO

Government Medical College and Hospital, Kottayam, Kerala, India, Pin: 686008.

AUTHOR'S CONTRIBUTION

Dr. Meriya Zacharia contributed to the development of the protocol, conducted the research and data collection, and authored the article. Dr. Seena P contributed to development of protocol, intellectual content, and authored the article. Dr. Kiran Shaj conducted the research and data collection, statistical analysis, and authored the article; Dr. Neikhrietsonuo Kesiezie contributed in designing the study and authored the article.

CONFLICT OF INTEREST

Nil.

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Nil.

REFERENCES

1. Walsh S, Lee HY, Creamer D. Severe cutaneous adverse reactions to drugs. In: Griffith CE, Barker J, Bleiker T, Chalmers R, Creamer D, editors. Rook's Textbook of Dermatology. 9th ed. Vol. 2. Oxford: Wiley-Blackwell; 2016. p. 119.1-23.
2. Kumari R, Timshina DK, Thappa DM. Drug hypersensitivity syndrome. Indian J Dermatol Venereol Leprol 2011;77:7-15. doi: 10.4103/0378-6323.74964, PMID 21220873
3. Yang JJ, Lei DK, Ravi V, Maloney NJ, Crew A, Worswick S. Overlap between hemophagocytic lymphohistiocytosis and drug reaction and eosinophilia with systemic symptoms: A review. Int J Dermatol 2021;60:925-32. doi: 10.1111/ijd.15196
4. Kardaun SH, Sekula P, Valeyrie-Allanore L, Liss Y, Chu CY, Creamer D, *et al.* Drug reaction with eosinophilia and systemic symptoms (DRESS): An original multisystem adverse drug reaction. Results from the prospective RegiSCAR study. Br J Dermatol 2013;169:1071-80. doi: 10.1111/bjd.12501, PMID 23855313
5. Bhargava P. Anticonvulsant hypersensitivity syndrome study of 60 cases. Indian J Dermatol Venereol Leprol 2001;67:317-9. PMID 17664787
6. Sasidharanpillai S, Riyaz N, Rajan U, Binitha MP, Khader A, Mariyath OK, *et al.* Drug reaction with eosinophilia and systemic symptoms: Observations from a tertiary care institution. Indian J Dermatol Venereol Leprol 2014;80:221-8. doi: 10.4103/0378-6323.132249, PMID 24823399
7. Picard D, Janela B, Descamps V, D'Incan M, Courville P, Jacquot S, *et al.* Drug reaction with eosinophilia and systemic symptoms (DRESS): A multiorgan antiviral T cell response. Sci Transl Med 2010;2:46ra62. doi: 10.1126/scitranslmed.3001116, PMID 20739682
8. Walsh S, Diaz-Cano S, Higgins E, Morris-Jones R, Bashir S, Bernal W, *et al.* Drug reaction with eosinophilia and systemic symptoms: Is cutaneous phenotype a prognostic marker for outcome? A review of clinicopathological features of 27 cases. Br J Dermatol 2013;168:391-401. doi: 10.1111/bjd.12081, PMID 23034060
9. Marcia L. Phenytoin for seizure prophylaxis after traumatic Brain Injury in children. Pediatr Pharmacother 2005;11:1-4.
10. Griebel ML, Kearns GL, Fiser DH, Woody RC, Turley CP. Phenytoin protein binding in pediatric patients with acute traumatic injury. Crit Care Med 1990;18:385-91. doi: 10.1097/00003246-199004000-00007, PMID 1969339
11. Alimardani S, Sadrai S, Masoumi HT, Salari P, Najafi A, Eftekhar B, *et al*. Pharmacokinetic behaviour of phenytoin in head trauma and cerebrovascular accident patients in an Iranian population. J Res Pharm Pract 2017;6:217-22. doi: 10.4103/jrpp.JRPP_17_58, PMID 29417081
12. Husain Z, Reddy BY, Schwartz RA. DRESS syndrome: Part I. J Am Acad Dermatol 2013;68:693.e1-14. doi: 10.1016/j.jaad.2013.01.033
13. Abraham AP, Vidyasagar A, Lakshmanan J, Nair S, Joseph M. Phenytoin toxicity in patients with traumatic brain injury. Neurol India 2014;62:285-9.