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Study of Clinico-epidemiological features and changing trends of fixed-drug eruption (FDE) in north India

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Abstract

Background: A fixed-drug eruption (FDE) is an immune mediated unique cutaneous adverse drug reaction characterised by recurrent lesions at the same site after re-exposure to offending agent**.**

Methods: The aim of present study was to study clinico-epidemiological features and to identify changes and trends of fixed drug eruptions with regard to causative drug or patient risk factors.It was a hospital based study carried in tertiary care hospital of North India from June 2018 to June 2020 in which patients with clinically diagnosed cases of FDE were studied.

Results: A total of 60 patients in age group of 6years to 76 years were studied. There were 36 males and 24 females (M:F 1.3). The most patients were in age group 31-40 years (40%) followed by age group 21-30 years (30%). The lag period between drug intake and appearance of lesion ranged 0-12 days.The most common site was extremities(53.33%) followed by lips(23.33%) and genitalia(16.67%).Number of lesions extending from one to more than five with most patients presenting with single lesion. Well defined erythematous to hyper pigmented macule/plaque was most common presentation(80%) followed by bullous. Antimiciobials(58.33%) and Non steriodal anti-inflamatory drugs(NSAIDS) (26.67%) were most common agents implicated. Most patients with extensive FDE had previous history of FDE.

Conclusion: The high percentage of patients with recurrent FDEs with increasing number of lesions and sometimes more severe reaction with re-adminstration underlines the fact of importance of recognizing an FDE as well as avoiding adminstration of same or structurally related drug to a patient who once developed FDE.

Keywords: Fixed Drug Eruption (FDE), Immune mediated, Cutaneous Adverse Drug Reactions (CADRs).

Introduction

A fixed- drug eruption (FDE) is an immune mediated cutaneous adverse reaction that often recurs at the same location after exposure to the same drug and is clinically characterised by sharply demarcated ,round or oval itchy plaques of erythema and edema which becomes dusky violaceous or brown. It can be seen in all age groups including infants and elderly[1]. Its incidence varies from 2.5% to a high of 22% of all patients with cutaneous adverse drug reactions (CADRs). The number of diagnosed FDE cases is steadily increasing, due in part to increased awareness by physicians, but also because of increased use of drugs[2].

Diagnosis of FDE is often established clinically. However, histopathological analysis can be helpful for the diagnosis. Oral provocation tests can be performed to confirm the

diagnosis of FDE ; however, these are not recommended because of risk of generalised bullous eruption[3,4].

Materials and methods

This was a hospital based study conducted in tertiary care hospital in North India. All cases of FDE diagnosed (clinically) between June 2018 to June 2020 were analysed for patient characteristics, type and number of lesions of FDE and suspected drug. The aim of the study was to study clinico-epidemiological features of FDE and to identify any change in trend of FDE with regard to causative drug or patient risk factors.

Results

A total of 60 patients with FDE were reported during the study period of 2 years from June 2018 to June 2020. Among these 60 patients 34 were males and 26 females (male: female ratio of 1.3). The age of our patients ranged from 6 years to 76 years. Majority of patients were in age group of 31 to 40 years (24 pts 40%), followed by 21 to 30 years (18 pts 30%). The lag period between intake of suspected drug and onset of eruption ranged from 0 (lesions appeared on the same day) to 12 days. Twenty two(36.67%) of 29 patients who developed lesions on the same day had previous history of FDE. (Table 1)

Clinical Pattern								Total Number of Cases
Gender	Male			Female				60(100%)
	34(56.67%)			26(43.33%)				
Age Distribution (Years)	0-10	11-20	21-30	31-40	41-50	>50		60(100%)
	1(1.67%)	2(3.33%)	18(30)%	24(40%)	10(16.6%)	5(8.3%)		
Number of Lesions	one Lesion		2-5 Lesions		>5 Lesions			60(100%)
	28 (46.7%)		24(40%)		8(13.3%)			
Site of Lesions	Upper Limb(UL)	Lower Limb(LL)	Both(UL and LL)	Lips	Genitalias	Trunk	Head& Neck	60(100%)
	10(16.6%)	8(13.3%)	14(23%)	14(23%)	10(16.6%)	2(3.3%)	2(3.3%)	

Table 1: Clinical characters of patients with Fixed Drug Eruptions

The most common sites affected were extremities (Image1) (32pts 53.33%), lips (Image 2) (14 pts 23.33%), genitalia (Image 3) (10pts 16.67%), trunk (2pts 3.33%) and head and neck excluding lips (2pts 3.33%).

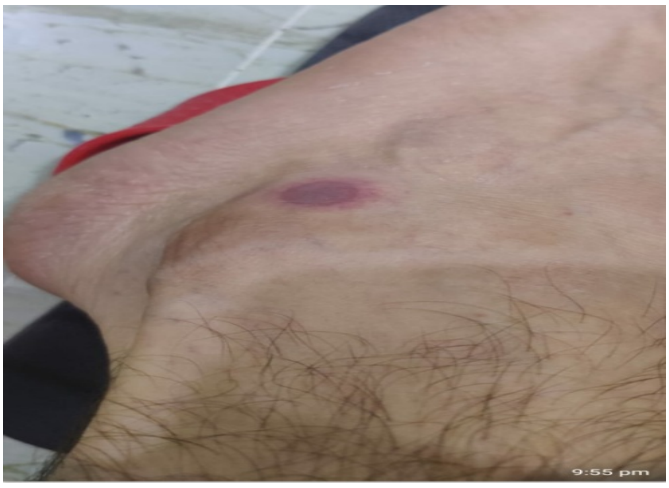

Figure 1

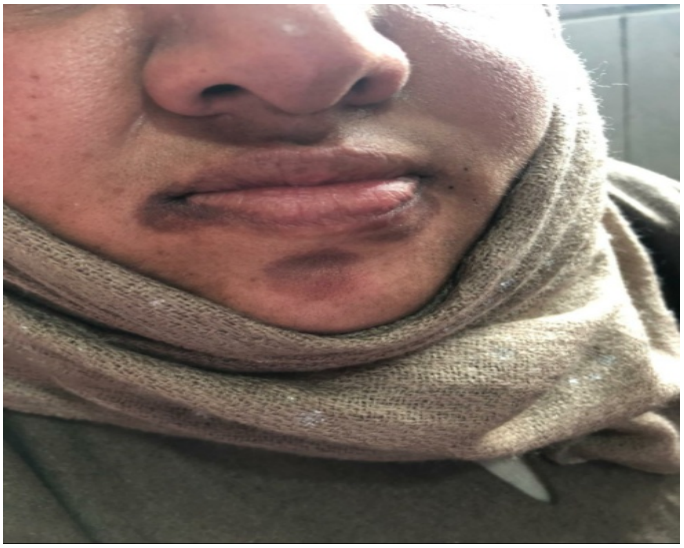

Figure 2

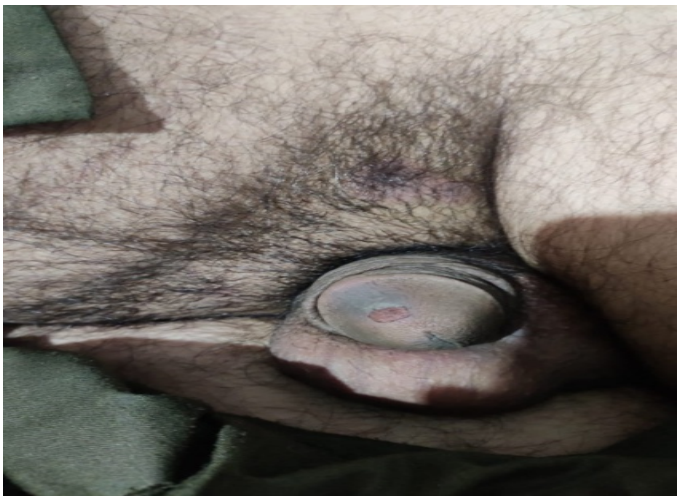

Figure 3

The number of FDE lesions in individual patient varied from 1 to more than 5, with 28 patients (46.7%) presenting with single lesion, 24 patients (40%) with 2-5 lesions and 8 patients (13.3%) had 6 or more lesions and among them three patients had extensive FDE. Of the 32 patients with 2 or more lesions 28 patients had previous history of FDE, whereas only 10 out of 28 patients with single lesion had previous history of FDE. Most of patients 48 (80%) presented with well-defined erythematous to hyperpigmented macules and /or plaques(Image 4), bullous FDE (Image 5) was seen in 8 (13.33%) and 4 (6.67%) patients hadan overlap of plaque and bullous lesions.

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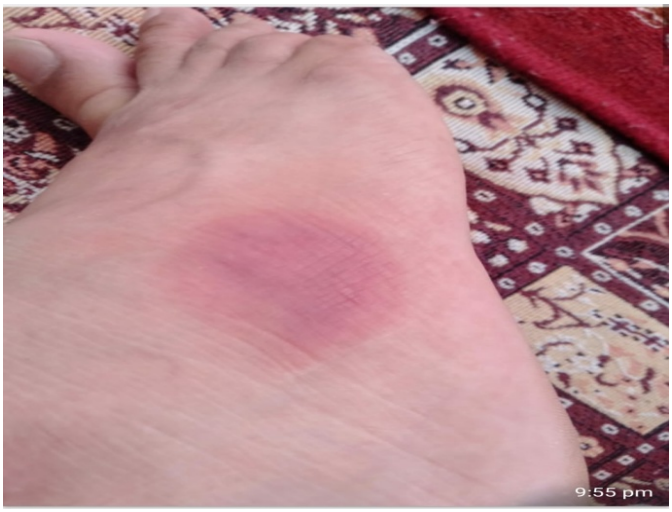

Figure 4

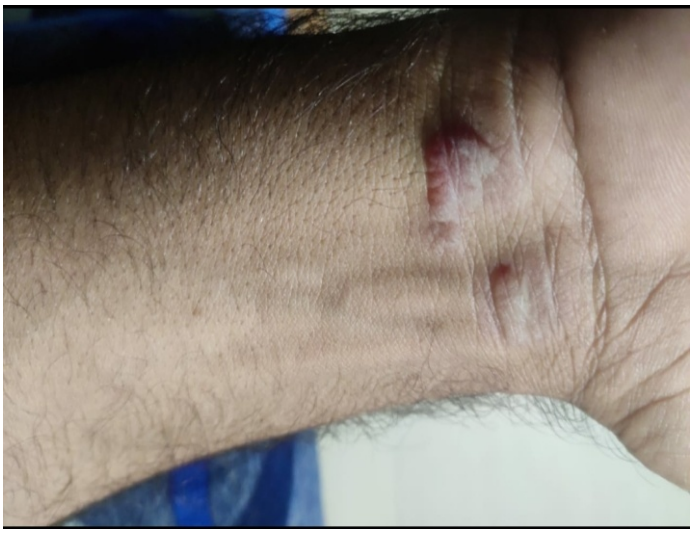

Figure 5

Antimicrobials (58.33%) and nonsteroidal anti-inflammatory drugs (26.67%) were the most common drugs implicated in majority of patients. Among the antimicrobials antibacterial agents (flouro-quinolones) and agents with dual antibacterial and antiprotozoal action (nitro-imidazoles) were most common drugs involved followed by antifungals (8.33%). Other drugs responsible for FDE were loperamide (2), drotaverine (2),phenytoin(2) pregabalin and methycobalamin (1), levocetrizine (1) and methotrexate (1). Out of 3 patients with extensive FDE, two were due to ciprofloxacin and other one with aceclofenac and paracetamol combination. All three patients with extensive FDE had past history of FDE. (Table 2).

Type of Drug Implicated		Number of Patients affected	Percentage among total cases
Antibacterial and Antiprotozoal	Ofloxacin + ornidazole	10	16.67%
	Ciprofloxacin	4	6.66%
	Ciprofloxacin + Tinidazole	3	5%
	Ofloxacin	3	5%
	Norfloxacin	2	3.33%
	Norfloxacin+ Tinidazole	2	3.33%
	Cefixime + Ornidazole	2	3.33%
	Trimethoprim + sulfamethoxazole	4	6.66%
Anti Fungal	Terbinafine	2	3.33%
	Itraconazole	2	3.33%
	Fluconazole	1	1.67%
NSAIDS	Paracetamol + aceclofenac	4	6.67%
	Paracetamol + Ibuprofen	2	3.33%
	Paracetamol + diclofenac	2	3.33%
	Etoricoxib	4	6.67%
	Nimesulide	2	3.33%
	Aceclofenac	2	3.33%
Others		9	15%
Total		60	100%

Table 2: Types of drugs implicated in patients with Fixed Drug Eruption

Discussion

The fixed drug eruptions (FDE) occur in both sexes and all age groups. A slight male predominance has been reported in some studies[5,6,7]. Jhaj et al,2018 in their case series of 50 patients with FDE, one (62%) were males. Similarly Jung et al,2014 and Sehgal et al,2006 reported

slight male preponderance in their studies. In our study also there was male predominance of patients (56.67%) with (male:female ratio of 1.3:1). However, there are few reports of female dominance[8,9]. The most common patients affected in our study were in age group between 21 -40 years (70%). with only 5% patients only in age group below 20 and 8.3% patients above 50 years of age.The results of our study are consistent with many previous studies[5,10]. Sixty six percent patients in a case series by Jhaj et al, were in age group between18-45 years. However, in a study by jung et al, more patients(47.8%) were in age group 40 and above and 31.3% patients were in in age group below 20 years.

The most frequently affected sites in our study were extremities (53.33%), lips (23.33%) and genitalia (16.67%). All these sites are recognised as common sites of involvement in several studies in past[1,5,8].

Antimicrobials and non steroidal anti-inflamatory drugs were the most common drugs involved in our study with 58.33% and 26.67% respectively, which is consistent to many previous studies[1,11,12]. Among the antimicrobials flouroquinolones and nitroimidazoles were most commonly involved. This is because of increasing use of these drugs over the counter in this part of country and overall use of these antibiotics by general physicians[9,13,14].Similarly there were cases of FDE with antifungals due to increased use in combinations because of increased prevalence of dermatophytosis in india[15,]. The cases of FDE with trimethoprim –sulfamethaxozole and doxycyclin were very few although previously among common drugs causing FDE could be due to decrease in prescription of these antibiotics[6]. The other drugs implicated in our study were phenytoin[16], loperamide[17], ivermectin[18], mycophenolate[19], levocetrizine[20,21,22,] and pregabalin plus methylcobalmin combination[23],all of which have been recognised in past as possible causes of FDE.

FDE are well known for their recurrent nature. Many authors have reported a high proportion of recurrent FDEs[14]. In our study, 38 cases (63.33%) had past history of FDE. In few patients there was cross reaction between ciprofloxacin and ofloxacin – that was FDE due to ciprofloxacin in patient with history of FDE to ofloxacin and vice versa. Similarly there was cross reaction between ornidazole and metrinidazole. These type of cross-reaction have been reported previously also[24,25,].

The most common type of presentation was well defined erythematous to hyperpigmented macule/s and or plaque/s (80%), followed by bullous (13.33%), and mixed of above two (6.67%). Most patients had more than one lesion (53.33%) especially those with recurrent FDE. The majority of patients(22 of 29 or 75.8%) whose lesions appeared on the same day of suspected drug intake had history of FDE. Furthermore, 87.8% of patients with multiple lesions had previous history of FDE while only 35.7% of patients with single lesion had such history in past. Also all three patients with extensive lesions had history of FDE in past. It might be concluded that thosepatients who had previous history of FDE were more likely to have an earlier onset and more number of lesions and more severe FDE. The increase in number of lesions and severity of lesions on re-exposure is related to the pathophysiology of FDE. Intraepidermal CD8 T cells seem to play important role. These cells remain quiescent in a primed state in healed FDE lesions[26]. When a causative drug or a structurally related one is re-administered, these primed CD8 T cells are activated and release interferon gamma from cytotoxic granules. Mast cells and neutrophils also take part in pathogenesis[27].

Conclusion

The high percentage of patients with recurrent FDEs and more number of lesions and sometimes more severe reaction with re-administration underlines the important fact of recognizing an FDE as well as avoiding administration of same or structurally related drug to a patient who once developed FDE. The patient should be given a card by medical practitioner displaying reaction to a specific drug as patient may visit multiple health facilities and practitioners and practitionare should take a good history of any drug reaction in the past as prevention is the key.

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