

ORIGINAL ARTICLE

Clinical features, culprit drugs, and allergology workup in 41 cases of fixed drug eruption

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Abstract

Background: Fixed drug eruption (FDE) represents a drug-related cutaneous reaction. Many drugs been associated with this clinical entity, with continually evolving documentation of implicated agents and clinical presentations. A bullous form can occur although it is rare.

Objectives: To assess the epidemiological and clinical characteristics of FDE.

Methods: We retrospectively analysed all FDE cases who presented to the Clinical Pharmacology Department at the University Hospital, Monastir, Tunisia, for allergy workup.

Results: The mean age of the 41 confirmed FDE cases was 43.8 ± 15.5 years. The time between first lesion onset and FDE diagnosis was less than 1 month for 13 patients (31.7%). Fifteen patients had bullous lesions. The upper limbs were the most common location (65.9% of cases). The patch tests were positive in 27 cases; a provocation test yielded a positive response in the four cases tested. Nonsteroidal anti-inflammatory drugs (NSAIDs) were involved in 51.2%, antibiotics in 24.4%, and other analgesics in 19.5%. The most common offending drug was mefenamic acid in 24.4% of cases. Bullous lesions were significantly associated with paracetamol intake ($P = .014$; odds ratio 16.7; 95% confidence interval: 1.76-158).

Conclusions: NSAIDs and antibiotics were the most implicated in inducing FDE; paracetamol was associated with bullous lesions.

KEYWORDS

epidemiology, fixed drug eruption, oral rechallenge, patch test

1 | INTRODUCTION

Fixed drug eruption (FDE) is a relatively common drug-induced skin eruption characterized by one or multiple skin lesions manifesting as erythematous and edematous oval plaques, sometimes bullous. FDE commonly occurs on the lips and genitalia, but may affect any area of the body. The eruption begins typically a few days after drug intake

and resolves leaving residual pigmentation in the involved site.¹ These plaques are termed "fixed" because they reappear at the same site; however, new lesions may emerge in other locations as well after further administration of the culprit drug. The most often implicated drugs are sulfonamides, tetracyclines, nonsteroidal anti-inflammatory drugs (NSAIDs), and paracetamol.¹ Although the pathogenic mechanism underlying FDE remains unclear, involvement of a T-cell-mediated

reaction is likely. The oral drug rechallenge (oral provocation test) is considered the gold-standard diagnostic tool. Skin tests are reliable and safe diagnosis methods in patients with FDE. To date, only few cohort studies on FDE have been published and all of them were descriptive.¹⁻¹⁴ Thus, the aim of this study was to assess the epidemiological, clinical, and chronological characteristics of FDE, indicate the implicated drugs, and determine the degree of association between intake of the drug and specific clinical features.

2 | METHODS

In this study, we retrospectively enrolled all cases of FDE that presented to the Clinical Pharmacology Department at the University Hospital of Monastir over a 14-year period (2004-2018). The FDE diagnosis was defined by a typical clinical manifestation (erythematous bright red or dusky red macules that might evolve into an edematous plaque with residual grayish or slate-colored hyperpigmentation) or histopathological evidence for FDE.

The culprit drug was identified by a meticulous history review and performing an allergy workup in terms of patch and oral provocation tests. The patch tests were performed according to the European Network Drug Allergy recommendations. Test samples were crushed tablets of the suspected drug (10%-30% in petrolatum [pet.]). The tests were applied under occlusion for 48 hours in Finn Chambers (SmartPractice, Canada) on residual FDE lesions (lesional patch test). The result was read 2, 3, and 4 days later. The patch tests were considered positive if there was erythema, pruritus, or infiltration around

the involved site. The oral provocation tests were performed after obtaining informed consent of the patients when the patch test result was negative. On day (D) 1, the patient was given one-fourth to one-half of the therapeutic dose. If there was no reaction for 24 hours, the patient was given full therapeutic dose for 3 days and if there was still no reaction, the test was considered negative.

Ethical approval was obtained from the local committee. Informed consent was obtained from all patients included in this study. Statistical analysis of the data was performed using the SPSS 21.0 software (IBM, Armonk, New York). An univariate analysis and multivariable logistic regression were conducted to compare gender, age, and culprit drug or drug group between patients having one or multiple lesions on the one hand and between those having bullous or non-bullous lesions on the other hand. The association between bullous and multiple forms of FDE and drugs was calculated using the odds ratio (OR) with 95% confidence intervals (CIs). Each pharmacological class was compared with all other classes. A *P*-value <.05 was considered statistically significant.

3 | RESULTS

A total of 41 patients, 24 (58.5%) females and 17 (41.5%) males, were included in this study. The mean age was 43.8 ± 15.5 years (range: 10-75 years). Table 1 summarizes the clinical characteristics of the enrolled patients. A total of 25 cases (61%) were diagnosed by their typical clinical manifestation, and 16 (39%) were diagnosed through histopathological documentation. Twelve patients (29.3%) had FDE

TABLE 1 Offending drugs in fixed drug eruption (FDE)

Drug-induced FDE	n	%	Number of skin tests done	Number of positive skin tests (%)
Nonsteroidal anti-inflammatory drugs	21	51.2	20	17 (85)
Mefenamic acid	10	24.4		
Piroxicam	9	22		
Acetyl salicylic acid	1	2.4		
Celecoxib	1	2.4		
Antibiotics	10	24.4	6	4 (66.7)
Amoxicillin	3	7.3		
Levofloxacin	2	4.9		
Ciprofloxacin	1	2.4		
Doxycycline	2	4.9		
Sulfaguanidine	1	2.4		
Vancomycin	1	2.4		
Paracetamol	7	17.1	6	4 (66.7)
Codeine	1	2.4		
Anticonvulsants	2	4.9	2	1 (50)
Carbamazepine	1	2.4		
Phenobarbital	1	2.4		
Total	41	100	34	27 (79.4)

for the first time and 29 (70.7%) had at least two episodes. The FDE was solitary in 10 patients (24.4%), scattered (two to five lesions) in 28 (68.3%), and generalized in three (7.3%). The delay between drug intake and initial FDE symptoms was within 2 days in all cases. The time between onset of the first lesion and the establishment of FDE diagnosis was less than 1 month in 13 patients (31.7%), between 1 and 6 months in 10 (24.4%), and more than 1 year in 18 (43.9%). Fifteen patients (36.6%) had bullous lesions that were scattered in 11 cases. The upper limbs were the most common location (65.9%), followed by the lower limbs (31.7%), the face and the scalp (29.3%), and the trunk (26.8%), with possibility of multiple occurrences. Involvement of mucous membranes was noted in three cases.

Patients were tested to a single drug highly suspected as culprit in view of the temporal relationship between intake and FDE occurrence. Patch tests were performed in 34 patients. They were positive in 27 cases and negative in the seven remaining ones. NSAIDs were the drugs most associated with positive skin tests (63%) followed by paracetamol (14.8%). Four of patients with negative skin test results underwent a provocation test with a positive response in all cases. Most patients with a positive allergological workup developed a reactivation of lesional FDE; only one patient developed a bullous FDE after a patch test. This patient initially developed a bullous eruption after celecoxib intake. A provocation test was not performed in the remaining three patients because they had bullous eruptions. A positive accidental rechallenge of the culprit drug was observed in four patients in whom allergy workup was not performed (Figure 1). Adverse reactions were observed in three patients after the allergy workup. Two patients observed reactivation of old lesions after patch

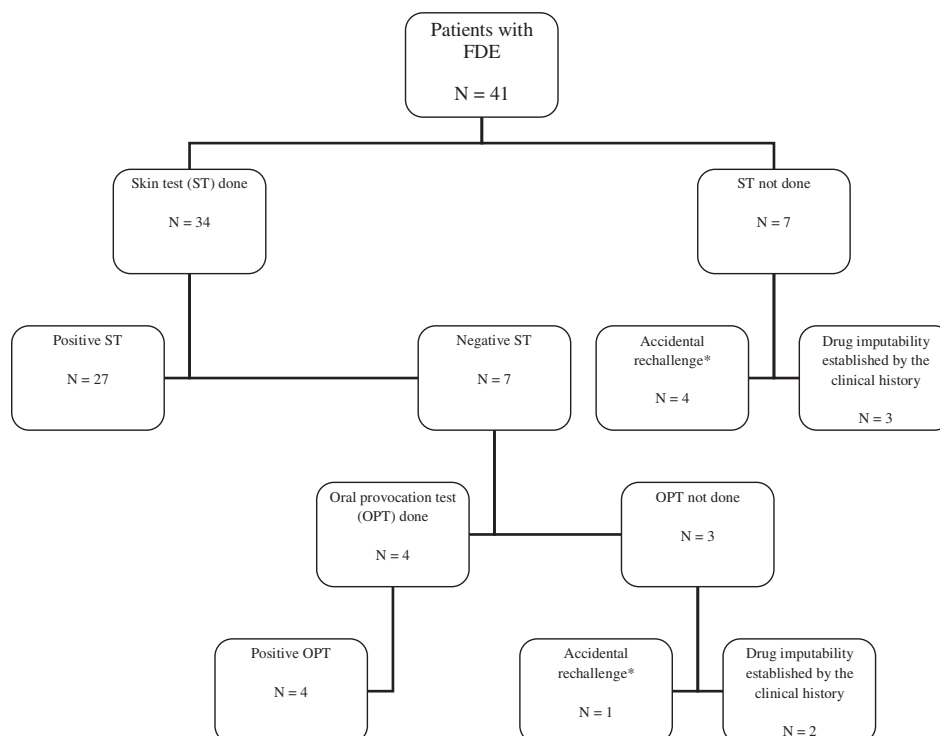
testing. One patient had developed new lesions at other sites after a drug rechallenge.

The offending drugs were identified in all patients (Table 1). NSAIDs were involved in 51.2% ($n = 21$) of patients, antibiotics in 24.4% ($n = 10$), and analgesics in 19.5% ($n = 8$). The most common offending drugs were mefenamic acid in 10 (24.4%) cases followed by piroxicam in nine (22%) cases and paracetamol in seven (17.1%) cases. Amoxicillin ($n = 3$) and fluoroquinolone ($n = 3$) were the most incriminated antibiotics in our series followed by doxycycline ($n = 2$).

Bullous lesions were significantly associated with paracetamol intake ($P = .014$; OR 16.7; 95%CI: [1.76-158]). Nonbullous FDEs were less common with intake of NSAIDs ($P = .037$; OR 0.23; 95%CI: 0.057-0.91). Multiple FDE lesions were not found to be statistically significantly correlated with age, gender, or causative drugs (Table 2). Regarding localization, the limbs and the trunk were involved in 68.6% of NSAID-induced FDE.

4 | DISCUSSION

This study demonstrates, based on a large case series of FDE, that this cutaneous drug reaction is mainly induced by NSAIDs and that the allergy workup is efficient to identify the culprit drug. We also showed that paracetamol was associated with a significant risk of the bullous form of FDE. To our knowledge, 15 case series including patients with FDE have been published until now. The largest one by Mahboob and Haroon included 450 patients.¹ Contrary to most reports,²⁻⁷ our study showed a slight female predominance. Similar results were also reported by Brahimi et al⁸ and Andrade et al.⁹ In addition, we found



* All accidental rechallenges with reactivation of FDE

FIGURE 1 Results of skin tests and oral provocation tests. FDE, fixed drug eruption

TABLE 2 Association between clinical features of fixed drug eruption (FDE) and causative drugs and demographic data

Outcome	Explanatory factor	P-value	Odds ratio	95%CI
Bullous FDE (n = 15)	Gender	.74	1.40	0.38-5.06
	Age	.17	1.94	0.75-5.02
	Causative drugs			
	NSAIDs	.03	0.22	0.05-0.91
	Paracetamol	.01	16.7	1.75-158.12
	Antibiotics	1	1.21	0.28-5.23
Multiple FDE (n = 31)	Anticonvulsant	.52	n.c.	–
	Gender	.71	0.63	0.15-2.65
	Age	.20	–	–
	Causative drugs			
	NSAIDs	.71	1.6	0.37-6.80
	Paracetamol	.66	2.16	0.22-20.49
	Antibiotics	.22	0.36	0.07-1.69
	Anticonvulsant	.99	n.c.	–

n.c., not calculable; NSAID, nonsteroidal anti-inflammatory drug.

that more than half of our patients were aged between 20 and 50 years, which is in accordance with some published data that confirm that FDE is frequent in young adults.^{1,5,8}

Mahboob and Haroon¹ reported that 31% of their patients were diagnosed within 1 year of onset of the first episode of FDE. The time between the first lesion onset and the establishment of FDE diagnosis was more than 1 year in nearly half of our patients. This might also be responsible for multiple episodes of FDE in the majority of our patients (70.7%). Indeed, we found that most patients (75.6%) presented multiple lesions, a finding which is consistent with some previous reports.^{1,3,5}

Generalized bullous FDE is a rare variant of FDE with blister formation and constitutes a potentially serious condition. This type of FDE may appear after repeated exposures to the offending drug.⁶ About one-third of our patients presented with a bullous FDE which is in accordance with many reports.^{2,4,6,8} For example, Jung et al² noted a bullous lesions in 19 of 52 patients (36.5%) with FDE. Conversely, Kavoussi et al⁵ found that only 6.7% of their patients developed a bullous eruption. Paracetamol intake, but not age or gender, was identified to be associated with a significant risk of bullous FDE onset. Several studies reported that FDE may preferentially involve certain anatomical sites such as the limbs, trunk, genitalia, or lips.^{1,4,10} The upper limbs are the common site for FDE in our study, which corroborates the findings of Kavoussi et al and Jung et al.^{2,5} In addition, a possible association between the offending drug and the localization was reported previously.¹¹ In the current study, NSAID-induced FDE was mostly localized on the extremities. However, Özkaya-Bayazit¹¹ showed that NSAIDs involved the lips more frequently.

Interestingly, the patch tests allowed us to identify the culprit drug inducing FDE (27/34 tested patients) in 79.4% and for all tested

patients with bullous FDE (15 cases). Therefore, this tool can be helpful and safe in screening for the causative drug, especially in the bullous form. Previous reports support our findings.^{12,15} Controlled oral provocation and accidental oral rechallenge were positive in four and five cases, respectively. Certainly, this latter test represents the gold standard in FDE diagnosis and workup, but this tool could be associated with the emergence of new flares and the occurrence of more severe episodes.^{12,13}

In this study, NSAIDs were the most common causative drugs (51.2%) followed by antibiotics (24.4%). This finding is in accordance with other recent studies such as the one conducted by Heng et al⁶ and Andrade et al⁹ but not with the series of Mahboob and Haroon, in which NSAIDs represented only 9.6%.¹ However, most reported series showed that antibiotics were the most incriminated drugs.^{1,3,4,10,13,14} Andrade et al⁹ reported that NSAIDs were the most frequently involved drugs (90.4%) and the list included almost all groups (eg, propionics, arylcarboxylics, coxibs), but not fenamates. In our study, the most involved NSAID was mefenamic acid, which is a fenamate. Among antibiotics, tetracyclines and sulfonamides were the most frequently implicated groups in inducing FDE, especially in Asian populations.^{4,11} Recently, fluoroquinolones have become increasingly associated with FDE.^{4,11,14} In our case series, we observed that antibiotics were the second most common elicitors of FDE, with amoxicillin and fluoroquinolones being the agents most often implicated. Few cases of FDE related to amoxicillin have been described previously.¹⁶ Paracetamol was responsible for FDE in 17% of cases in our study. This drug was found to be an FDE inducer in most series with a frequency ranging from 1% to 15%.^{1,3,6,8,9,14} Moreover, we showed that paracetamol intake was significantly associated with the bullous variant of FDE. To our knowledge this finding has never been published previously. Finally, we observed two cases of FDE induced by anticonvulsants (ie, carbamazepine and phenobarbital). Some sporadic case reports described FDE induced by these two drugs.¹⁷⁻¹⁹

In conclusion, FDE diagnosis is often initially missed, leading to multiple episodes. This drug side effect seems to be a cutaneous adverse reaction mainly induced by NSAIDs and antibiotics. Paracetamol was found to be associated with a significant risk of bullous FDE. A patch test was efficient to determine the culprit drug and allowed to avoid provocation tests which could be associated with serious complications.

CONFLICTS OF INTEREST

The authors declare no conflict of interests.

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