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Common clinical patterns of fixed drug eruptions among Iraqi patients. A multicenter study.

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ABSTRACT

The purpose of this study was to assess the common clinical presentations of fixed drug eruption (FDE) among Iraqi patients. This is a multicenter cross-sectional descriptive study. One hundred and sixty patients who had FDE were seen in the Departments of Dermatology and Venereology at Al-Saddir Teaching Hospital and Ibn-Sena Teaching Hospital, Iraq, during the period from Oct. 2017 to Oct. 2018. A full history and clinical examinations were done for every patient. An oral provocation test was done for some patients. A skin biopsy was done for some patients to confirm the diagnosis. The age of the patients was 37.2 ± 16 years. The male-to-female ratio was 1.2:1. Most of our patients presented during the first week of rash appearance as they constituted 77.5% of patients. The shortest time of presentation after taking the causative medications was 30 minutes, whereas the longest duration from taking the insult medication was within two weeks. Multiple lesions were encountered in 76% of the patients and the upper extremities were the most frequently affected area in 26% of the patients. The most common morphological presentation in a patient with FDE was patches 49% and erosive type 17%. Itching was the most common symptom suffered by 42% of patients. The most common culprit agent of FDE was co-trimoxazole 47.5%. FDE is a common cutaneous disorder seen in dermatological outpatient clinics. Recurrent multiple patchy and erosive lesions are the commonest clinical presentation. The upper extremities are the most anatomical sites affected by FDE. Pruritus is the most commonest associated symptom.

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1. Introduction

Fixed drug eruption (FDE) is a relatively common skin disorder that facing dermatologists and physicians in daily clinical practice [1], presented clinically as well-demarcated, round, or oval pruritic plaques of erythema and edema becoming dusky violaceous or brown, and sometimes vesicular or bullous that recurs in the same site or sites each time after ingestion of the responsible drug [2]. The number of involved sites

may increase with recurrent intake of the drug. Usually, just one drug is a common culprit, although independent lesions from more than one drug have been described [3].

Brocq in 1894 was the first author to describe FDE due to antipyrine [4]. Since then several drugs have been administrated as causative agents by many researchers from different regions [5- 9].

The incidence of FDE is variable and tends to increase in the last decades [3], [10- 13]. The causes of fixed drug eruptions vary from country to country depending on the local patterns of drug use. Old drugs may be discontinued and replaced by new drugs that may have an unknown potential to cause this type of reaction. [13], [14].

A number of studies have suggested that cell-mediated immunity may play an important role in the pathogenesis of FDE, although the exact mechanism is still unknown [15]. Antibiotics, antiepileptics, nonsteroidal anti-inflammatory agents, and phenothiazines are the main categories causing fixed drug eruption, although several other agents and specific foods have also been reported as causative agents. Adverse reactions to medications are common and often manifest as a cutaneous eruption. They found that FDE is the commonest cause of cutaneous drug eruptions [16- 18].

The most common clinical variety of fixed drug eruptions is the pigmenting variety, which is usually presented as patches. Lesions are more common on the extremities than the trunk; the hands and feet, genitalia (glans penis), and perianal areas are favorite sites [19]. Local itching, burning, or pain at the site of lesions are related to the acute stage of the presenting episode but may be asymptomatic. FDE may manifest as pruritus vulvae or pruritus ani. Systemic manifestations are rare [20].

There is a long list of causative drugs manifesting fixed drug eruption and they are different in their frequencies from decades to decades and from country to country depending on the physician`s prescription, drugs availability, cost, effectiveness, and community health education [11], [12], [21].

2. Patients and Method

This is a cross-sectional descriptive study. A total of 160 patients who suffered from FDE were seen in the Department of Dermatology and Venereology at Al-Saddir Teaching Hospital, Missan, Iraq, and Ibn-Sena Teaching Hospital, Mosul, Iraq during the period from October 2017 to October 2018.

A full history was taken from every patient regarding the age, gender, residence, religion, duration of rash, the onset of the rash after taking the medication, site of lesion(s) other associated symptoms, number of attacks (recurrent or not), and personal or family history of fixed drug eruption. Physical and dermatological examinations were done for all patients concentrating on the morphology, distribution, color, and number of the lesions. An oral provocation test was done for some patients who had interested to know the definitive culprit. Lab investigations and skin biopsy were done for some patients to confirm the diagnosis. Photoshoots were taken using Sony Cyber-shot DSC-W300© after taking patient`s permission. Patients with unknown causative agents were excluded from the study.

Data are presented as mean ± SD and were analyzed using a non-paired T-test. The data were processed using statistical package SPSS version 23.

3. Result

A total of 160 patients with fixed drug eruption were seen, their ages ranged from 9 months-77 years with a

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mean age of 37.17 ±16.14 years. Males represented 88 (55%) of the patients while females were 72 (45%) patients, the male to female ratio was 1.2:1.

Most of our patients presented during the first week of rash appearance as they constituted 124 (77.5%) patients, 11 patients (6.87%) presented at the second week, and the rest (15.62%) patients were seen after the second week from the onset of the rash. Eighty-two (51.25%) patients were afflicted with FDE for the first time whereas the remaining 78 (48.75%) patients suffered recurrent episodes. Family history of FDE was founded in 20 (32.5%) patients.

The shortest time of presentation after taking the causative medications was 30 minutes, whereas the longest duration from taking the insult medication was within two weeks. A solitary lesion was encountered in 38 (23.6%) patients, 23 (14.28%) individuals had two lesions while 40 (24.84%) patients had more than 5 lesions. This study revealed that the upper limbs were the most commonly affected area, 78 (26.17%) patients, followed by the genitalia 55 (18.45%) and the face was the third site affected. The onset of the rash, number of the lesion(s), and distribution according to anatomical site(s) are shown in table 1.

Table (1): Frequency of cases according to the onset of rash, the number of lesions, and the site of involvement.

The onset of rash after taking the causative drug.	**No. of patients**	**Percentage of patients**
Day 1	120	75
Day 2	27	16.87
Day 3	9	5.62
Day 4	1	0.62
Day 5	1	0.62
Day 6	Zero	Zero
≥ Day 7	2	1.25
No. of lesions		
1	38	23.6
2	23	14.28
3	26	16.14
4	20	12.42
5	14	8.69
>5	40	24.84
Total	160	100%
Site of lesions		
Upper limbs	78	26.17
Genitalia	55	18.45
Face	53	17.78
Lower limbs	51	17.11

Trunk	36	12.08
Neck	17	5.7
Buttock	8	2.68
Total[#]	351	100%
[#]Same patients may had rash in more than one anatomical sites .		

The most common morphological presentation in a patient with FDE was patches (49.05%), followed by erosive lesions (16.98%). The frequency of other types of lesions like eczematous, bullous, targetoid, and cellulitis-like is depicted in figure 1. The predominant color of FDE lesions varies from erythematous, dusky red to brownish-black. The dusky red color was found in 67 (40.6%) cases, 51 (30.09%) had erythematous lesions and 47 (28.48%) had brown-black lesions. Variable clinical presentation of FDE is shown in Pictures.6-1

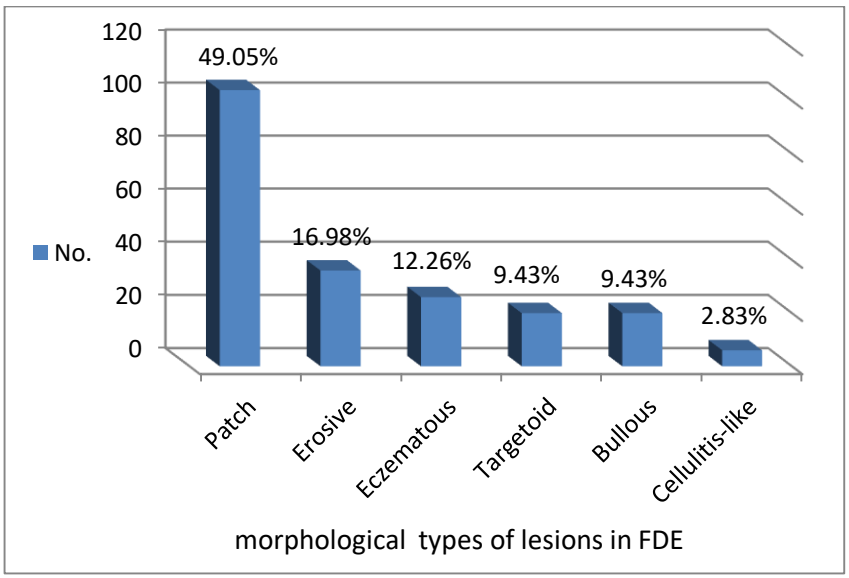
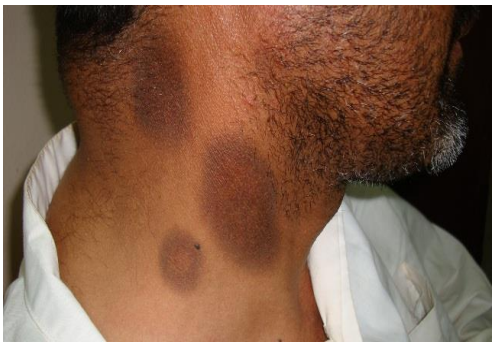
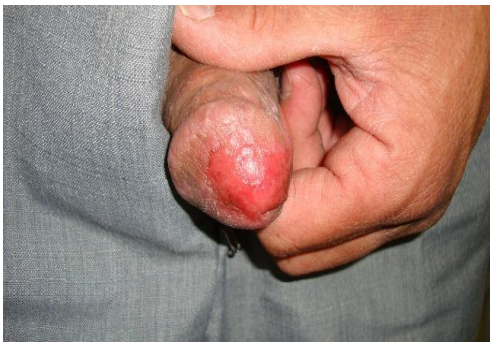


Figure (1): Distribution of patients with fixed drug eruption according to the morphology of lesions.



Picture (1): Patch lesion



Picture (2): Erosive lesion

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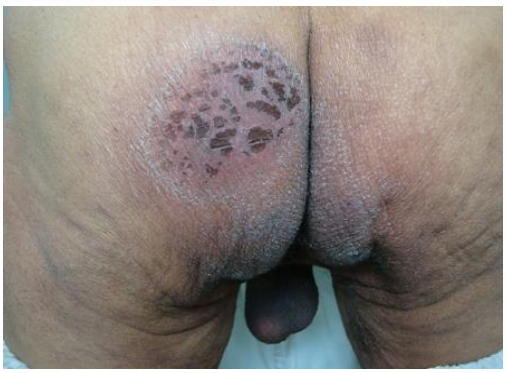
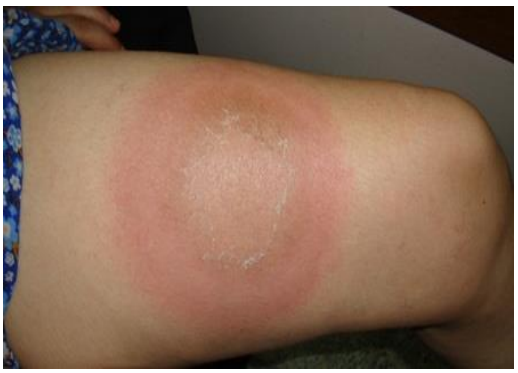
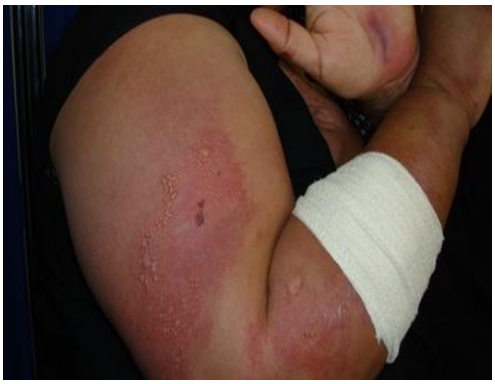


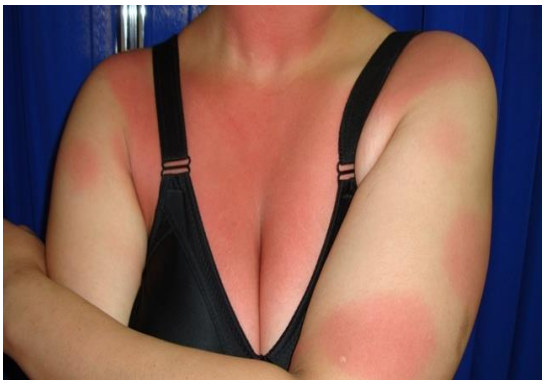
Picture (3): Eczematous lesion



Picture (4): Targetoid lesion



Picture (5): Bullous lesion



Picture (6): Cellulitis-like lesion

This study revealed that itching was the most common presenting symptom as suffered by (42.26%) patients, the next symptom was burning sensation as complained by 74 (38.14%) patients, pain was encountered in 20 (10.3%) patients and the rest of cases 18 (9.27%) were asymptomatic.

The most common causative agents of FDE in this study in order of decreasing frequency were cotrimoxazole (47.5%), paracetamol (12.5 %), mefenamic acid , and ciprofloxacin (10 %) for each. Other incriminated drugs are listed in table (2). For cotrimoxazole, the most common types of the lesion were patch which represented 51 (49.03%) cases, followed by erosive type 28 (26.92%), bullous 12 (1.15%), targetoid 8 (7.69%), eczematous 4 (3.84%) and cellulitis-like type was found in only 1 (0.96%) case. The associated symptoms were burning sensation 39 (33.33%), itching 36 (30.76%), pain 8(6.83%) while asymptomatic cases represented only 7 (5.98%) patients. The next is paracetamol clinically, the most common morphological lesions were patch which occurred in 12 (41.37%) of the cases, erosive in 6 (20.68%), bullous in 5 (17.24%), eczematous in 4 (13.79%), and targetoid in only 2 (6.89%) of the cases. Itching was suffered by 11 (44%) patients, burning sensation 8 (32%), pain in 5 (20%) and only 1 patient was asymptomatic. The third cause of FDE in this study was ciprofloxacin and mefenamic acid as each one was found to affect 16 patients. About ciprofloxacin clinically the most common type of lesions were patch 13 (68.42%), erosive 3 (15.78%), 2 (10.52%) targetoid, and only one (5.26%) case had an eczematous lesion. Itching was reported in 7 (36.84%) patients, burning sensation 6 (31.57%), pain 2 (10.52%), while asymptomatic cases were 4 (21.5%). For mefenamic acid the reported morphological types of lesions were: eczematous lesions 13 (52%), patches 7 (28%), targetoid and erosive 2 (8%) for each, and bullous. The commonest symptom accompanied was itching 11 (55%) cases, other reported symptoms were: burning sensation 6 (30%), pain 2 (10%), and 1 (5%) had no symptom.

Table (2): Number and percentage of fixed drug eruption cases according to the causative drug.

Drug	No. of patients	Percentage
Co-trimaxazole	76	47.5
Paracetamol	20	12.5
Ciprofloxacin	16	10
Mefenamic acid	16	10
NSAIDs*	11	6.87
Tetracyclines group**	6	3.75
Metronidazole	6	3.75
Penicillins	3	1.87
Captopril	3	1.87
Chlordiazopoxide	3	1.87
Acetyle salicylic acid	3	1.87
Folic acid	1	0.62
Acyclovir	1	0.62
Radioactive***	1	0.62
Hyocine	1	0.62
Sildenafil	1	0.62
Lentil	1	0.62

*NSAIDs included: Ibuprofen (3 cases), Diclofenac (4 cases), Naproxen (3 cases) and piroxicam (1 case).
**Tetracyclines included: Doxycycline (4 cases) and Tetracycline (2 cases).
***Technetium (Tc99).

4. Discussion

Many authors have found that fixed drug eruption (FDE) is a common dermatological problem with a given prevalence of 1% in outpatient clinics [14], and other investigators stated that FDE may account for as much as 16-21% of all cutaneous drug eruptions [22]. We have reached a similar finding in our study. We have encountered a total of 160 cases of FDE in the dermatological outpatient clinic in one year and FDE encountered about 1.01% of the total daily cases out of 65 patients per a day*, this finding makes FDE a relatively common dermatological problem.

Regarding age groups involved by FDE, many large studies have found that adults are more commonly affected than children and the third decade of life was the commonest age group involved [11]. Our study goes in parallel with these studies as we found the third decade of life was a common age group affected by FDE. Most series of patients with FDE found that males are more affected than females [5], [8], [23], [24]. However, one large study of 450 cases found the reverse (females more than males). Our study coincides with most published studies in that males are slightly more affected than females.

FDE may follow the consumption of the causative drug by a variable period of time ranging from half an hour to many weeks after insult [19], [20], [25]. We also had a similar finding regarding the time of presentation of FDE after the insult as we found the shortest duration was 30 minutes, whereas the longest duration was more than 2 weeks.

The number of lesions in FDE is usually variable as some authors stated that less than 6 lesions are a common presentation, [26] while other authors found that FDE usually presents with a single lesion [3] and others found that FDE may present with a different number of lesions ranging from 1 – 100 lesions [9]. We have found about one-quarter of our cases presented with a single lesion and approximately three-quarters of the patients had 5 lesions or less and only about one-quarter had multiple lesions (more than 5 lesions).

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Regarding the morphological types of rash in FDE, we have noticed different morphologies like patch, eczematous, targetoid, bullous, erosive, and cellulitis –like lesion, however, patchy lesions were the commonest form of presentation (about 50% of the cases) a finding which is similarly reported by many researchers [9], [11].

Different sites of the body may be involved by FDE and the commonest site involved is different according to individual study. The commonest sites affected in these studies were as followed, the lips [9], [11], the limbs [3], and the genitalia [20], [25], [27]. The extremities (upper and lower) were the commonest site involved in the present study as they constituted about 43% of all cases, whereas the genitalia was the next site and at the third rank was the face.

Pain, burning sensation, and itching may accompany FDE. About 82% of our patients were symptomatic with itching being the most frequent symptom. This finding is in contrast with that of [9] who found that 72% of the patients were asymptomatic. While it goes in agreement with that of [28] who found most of the cases were symptomatic.

* Local records of the total number of patients at Al-Saddir and Ibn-Sena teaching hospitals outpatients clinic of Dermatology and Venerology from October 2017 till October 2018 was about 15500 patients.

Most authors have found that co-trimoxazole is the commonest cause of FDE [29- 32]. Our result was in agreement with these studies as co-trimoxazole represented about half of our cases (47.5%), All clinical (morphological) patterns of drug reactions have been seen in cases of FDE caused by co-trimoxazole, however patchy and erosive lesions were responsible for about more than two-thirds of the cases.

Paracetamol is an over-the-counter medication that may be the most commonly consumed drug by the general population, however, only a few case reports were found regarding this agent as a cause of FDE. Two conflicting findings regarding the frequency occurrence of FDE caused by paracetamol, one study has found paracetamol as the commonest current cause of FDE seen by dermatologists in the U.K. [33], whereas other studies found that paracetamol (acetaminophen) is a rare cause of FDE [25], [34], [35]. Our result regarding paracetamol is more in parallel with the U.K. study as we found this drug was the second most common cause of FDE. The clinical pattern of FDE caused by paracetamol was somehow similar to that caused by co-trimoxazole in this series of patients, as patchy and erosive lesions were the commonest morphological patterns, however, with paracetamol the limbs were the commonest site of involvement, whereas the genitalia was less common.

5. Conclusions

FDE is a common pattern of cutaneous drug reaction seen in dermatological outpatient clinics. Multiple patchy and erosive lesions are the commonest clinical presentation. The upper extremities are the most common anatomical sites affected in FDE. Pruritus is a commonly associated symptom.

Limitations of this study

Despite the fact that this study was conducted in one of the major cities in Iraq, further studies are necessary to collect data from other hospitals and medical centers to provide a more precise picture of the frequency of FDE in Iraq, as well as to identify other culprit drugs that have not been identified in this study.

Conflict of Interests

The authors remark that they have no conflict of interest.

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