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FIXED DRUG ERUPTION WITH GENETIC ORIGIN

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ABSTRACT
Fixed drug eruption (FDE) usually appears as a solitary or a small number of pruritic, well circumscribed, erythematous macules that evolve into edematous plaques; these lesions typically recur at exactly the same sites. The lesions usually flare within 30 min to 8 h after drug intake. The sensation of burning often precedes the appearance of these lesions. The most commonly affected sites are the lip, palms, soles, glans penis, and groin areas. In some cases, the lesions become more widespread with bullous lesions and systemic manifestations, such as high fever and arthralgia, mimicking Stevens–Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN). FDE lesions occur more rapidly in patients intermittently receiving the causative drugs rather than those continuously receiving them. The previously involved sites do not necessarily flare with each exposure. We conducted a retrospective study over a period of 38 years which included 25000 patients. Out of these 25000 patients well recorded, 16% (4000) patients were of drug reactions. Out of these 4000 patients, 10% (400) patients were of FDE. Of these 400 patients, 8% (i.e. 32) had genetic origin in the immediate family member or cousins and other relatives; which speaks volumes for a genetic origin of FDE to various drugs and usually to the same drug in parents and siblings or brother's siblings.

INTRODUCTION
FDE usually appears as a solitary or a small number of pruritic, well circumscribed, erythematous macules that evolve into edematous plaques; these lesions typically recur at exactly the same sites. The lesions usually flare within 30 min to 8 h after drug intake. The sensation of burning often precedes the appearance of these lesions. The most commonly affected sites are the lip, palms, soles, glans penis, and groin areas. In some cases, the lesions become more widespread with bullous lesions and systemic manifestations, such as high fever and arthralgia, mimicking Stevens–Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN).[1] FDE lesions occur more rapidly in patients intermittently receiving the causative drugs rather than those continuously receiving them. The previously involved sites do not necessarily flare with each exposure.

Drug hypersensitivity reactions can occur with many drugs. The frequency, severity and clinical manifestations vary with each case. In India, the main drugs associated with drug reactions are sulpha and aspirin followed by tetracyclines, phenylbutazoe, NSAIDS, ampicillin and amoxycillin.[2] Aspirin ingestion can induce a wide range of clinically recognized allergic reactions, including aspirin- intolerant asthma (AIA), aspirin intolerant urticaria/angioedema (AIU), chronic rhinitis and anaphylaxis.[3] Dhar and Sharma have described seven patients with FDE due to Ciprofloxacin, two of which showed striking involvement of lips. These cases made up 8.75% of all cases of FDE seen by them for a specific period.[4]

A genetic predisposition to drug hypersensitivity has been suggested in various studies; and most significant genetic associations have been identified in the major histocompatibility complex for drugs such as abacavir, carbamazapine and allopurinol. However, hypersensitivity in one population may not be relevant for another population.[1] A strong association of the allelle HLA-B*5801 with the susceptibility of allopurinol - induced and HLA DPB1*0301 with aspirin - induced drug hypersensitivity respectively has been documented.[5] Apart from drugs, cashew nut is also classified as a potent allergenic food known to be responsible for causing severe and systemic immune reactions (e.g. anaphylaxis) when consumed by sensitised/allergic individuals that often demand epinephrine treatment and hospitalisation. Valk et al, in their study, have mentioned that the major cashew allergens are Ana o 1, Ana o 2 and Ana o 3.[6-9] The age of onset of cashew nut allergic symptoms varies between 2 months and 27 years with a mean of approxi-mately 3 years. Most allergic reactions to cashew nut, such as

other food allergies, manifest with skin lesions followed by respiratory and gastro-intestinal symptoms.[10-14]

FDE lesions initially appear when susceptible patients are sensitized to a particular drug. Such sensitization occurs more rapidly in patients intermittently receiving the causative drugs rather than those continuously receiving them. Thus, the period required for sensitization is highly variable depending on patients, ranging from a few weeks to several years. The previously involved sites do not necessarily flare with each exposure, which is known as the refractory period.[15] The duration of this period is also variable, lasting from a few weeks to several months.[16]

FDE usually appears as a solitary or a small number of pruritic, well circumscribed, erythematous macules that evolve into edematous plaques; these lesions typically recur at exactly the same sites with each administration of the causative drug, but upon the discontinuation resolve spontaneously, leaving hyperpigmentation. After clinical resolution, the lesions remain quiescent and typically present as gray–brown macules or plaques on the skin, mucous membranes, or on both for prolonged periods unless the causative drug is given. The lesions usually flare within 30 min to 8 h after drug intake; mean length of time from drug intake to the onset of symptoms is approximately 2 h. Sensation of burning often precedes the appearance of these lesions. Other common morphological patterns include urticaria/angioedema and erythema multiforme.

Although FDE can occur anywhere on the skin or mucous membrane, the most commonly affected sites are the lip, palms, soles, glans penis, and groin areas; interestingly, herpes simplex virus (HSV) is frequently reactivated in these areas of healthy individuals. In some cases, the lesions become more widespread with bullous lesions and systemic manifestations, such as high fever and arthralgia, mimicking Stevens–Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN). These FDE lesions become more numerous, and new lesions also develop on the previously uninvolved areas unless the causative drug is withdrawn.[1] Aspirin ingestion can induce a wide range of clinically recognized allergic reactions, including aspirin- intolerant asthma (AIA), aspirin- intolerant urticaria/angioedema (AIU), chronic rhinitis and anaphylaxis.[3]

The pathomechanism is complex and the clinical manifestations are due to chemical mediators like histamine, leukotrienes or prostaglandins released from sensitized tissue mast cells or circulating basophil leucocytes.[17]

Intraepidermal CD8þ T cells resident in the FDE lesions clearly have a major contributory role in the development of localized tissue damage.[15,18-21] T cells with an effector–memory phenotype preferentially migrate into the sites of infection, such as mucosal sites, and persist for long periods of time following infection, a finding consistent with FDE lesions initially appearing at sites of previously traumatized skin, such as burn scars and insect bites.[22-28] Tissue damage results when intraepidermal CD8þ T cells are activated to directly kill surrounding keratinocytes and release large amounts of cytokines such as IFNg into the local microenvironment.

In the resting state, intraepidermal CD8þ T cells remain quiescent but in a primed state, as evidenced by the expression of CD69. Upon drug intake, they are activated to release IFNg and cytotoxic granules into the local microenvironment. Mast cells localized in the vicinity of the epidermis also contribute to the activation of intraepidermal CD8þ T cells via the induction of cell adhesion molecules on surrounding keratinocytes through the action of TNFa. In fully evolved lesions, keratinocytes are killed by the direct action of intraepidermal CD8þ T cells in concert with CD4þ T cells recruited later on from the circulation. At the end of the immune response, T regulatory cells are recruited into the lesions and serve to inhibit severe immune responses mediated by intraepidermal CD8þ T cells and other infiltrating T cells; the majority of the expanded or activated population is removed by apoptosis. A proportion of intraepidermal CD8þ T cells prevented from undergoing apoptosis by IL-15 provided from keratinocytes leads to the persistence of a memory T cell population.[29]

Aspirin intolerance is likely to be associated with abnormalities in arachidonic acid metabolism, which include both the lipooxygenase (LOX) and cyclooxygenase (COX) pathways (arachidonic acid metabolic pathway via cyclooxygenase (COX) and lipoxygenase (LOX) pathway). Acetylsalicylic acid inhibits COX pathway and shunts arachidonic acid pathway towards LOX pathway and increased production of Cys- LTs such as LTC4, LTD4 and LTE4.[3]

RESULTS AND DISCUSSION

We conducted a retrospective study over a period of 38 years which included 25000 patients. Out of these 25000 patients well recorded, 16% (4000) patients were of drug reactions. Out of these 4000 patients, 10% (400) patients were of FDE. Of these 400 patients, 8% (i.e. 32) had genetic origin in the immediate family member or cousins and other relatives; which speaks volumes for a genetic origin of FDE to various drugs and usually to the same drug in parents and siblings or brother's siblings. Only 2 cases of 3rd generation FDE have been observed by us so far.

One patient was due to cashew nut; proven by challenge; for which reason we think it should be called fixed drug and fixed food reaction (FDFR).

One of the rich patients got his DNA tested from Bonfil Labs Colorado USA which showed association with

chromosome 6p. In India, sulpha and aspirin have a major chunk followed by tetracyclines, phenylbutazoe, NSAIDS, ampicillin and amoxycillin. Also, a case of cashew nut sensitivity was seen only three years back because prior to that we never suspected fixed reaction to foods. And we think that in the next decade or two when genetic studies may be available fully and cheaper in cost, then we might be able to find the exact gene responsible for causing FDE.

Also, we observed that nearly 85% of patients with genetic FDE were males and only 15% were females; for which there is no proper explanation. Hence, this field is unexplored and open for research.

S.no.	Relationship	Age at onset	Drug	Patch test	No. Of lesions	Site
1	Father	35	Sulfa drugs	+	Single	Scrotum/glans
	Son	2	Sulfa drugs	+	Single	Upper eyelid
2	Son	42	Norflox	+	Single	Scrotum/glans
	Father	67	Norflox	+	Single	Back
3	Mother	7	Sulfa drugs	+	Single	Back
	Son	5	Sulfa drugs	+	Single	Arm
4	Brother	25	Sulfa drugs	+	Single	Face
	Brother	20	Sulfa drugs	+	Multiple	Neck
5	Father	75	Metronidazole	+	Multiple	Oral mucosa
	Son	45	Metronidazole	+	Single	Arm/back
6	Brother	32	Levocetrizine	+	Single	Hand
	Sister	16	NSAIDS	+	Single	Arm
7	Cousin	32	Phenytoin	+	Single	Face
	Cousin	19	Aspirin	+	Single	Arm
8	Mother	28	NSAIDS	+	Multiple	Oral mucosa
	Son	15	NSAIDS	+	Single	Peno-scrotal junction
9	Father	29	Phenylbutazone	+	Single	Arm
	Son	20	Phenylbutazone	+	Single	Back
10	Mother	45	Mefenemic acid	+	Single	Arm
	Son	17	Mefenemic acid	+	Single	Back/trunk
11	Father	56	Tetracycline	+	Single	Glans penis
	Son	32	Tetracycline	+	Multiple	Neck
12	Father	36	Ampicillin	+	Single	Trunk
	Son	19	Amoxycillin	+	Single	Back
13	Father	34	Peroxicam	+	Single	Back
	Son	12	Peroxicam	+	Single	Arm
14	Mother	58	Acetylsalicylic acid	+	Single	Face
	Daughter	24	Acetylsalicylic acid	+	Single	Face
15	Brother	32	Sulfa drugs	+	Multiple	Face
	Brother	25	Sulfa drugs	+	Single	Neck
16	Father	25	Sulfa drugs	+	Single	Back
	Son	14	Sulfa drugs	+	Single	Tip of thumb
17	Son	10	Cetrizine	+	Single	Face
	Father	58	Loratidine	+	Single	Arm/trunk
18	Brother	15	Paracetamol	+	Multiple	Face/arm
	Brother	17	Aceclofenac	+	Multiple	Face/neck
19	Father	30	Metronidazole	+	Single	Back
	Daughter	17	Metronidazole	+	Single	Trunk
20	Son	15	Paracetamol	+	Single	Perioral
	Father	45	Aspirin	+	Single	Arm
21	Father	45	Rifampicin	+	Single	Face
	Son	22	Cetrizine	+	Single	Trunk
22	Grandfather	23	Loratidine	+	Single	Face/perioral
	Grandson	21	Loratidine	+	Single	Face/upper eyelid
23	Cousin (Brother)	15	Paracetamol	+	Single	Face
	Cousin (Brother)	26	Phenytoin	+	Single	Trunk
24	Father	12	Sulfa drugs	+	Single	Glans penis
	Son	25	Sulfa drugs	+	Single	Neck
25	Grandfather	25	ACE inhibitors	+	Single	Trunk

	Grandson	35	NSAIDS	+	Multiple	Face
26	Father	35	Paracetamol	+	Single	Face/neck
	Son	18	Ampicillin	+	Single	Trunk
27	Brother	25	Metronidazole	+	Single	Trunk
	Sister	42	Metronidazole	+	Single	Face/trunk
28	Mother	22	Fluconazole	+	Single	Arms/trunk
	Son	10	NSAIDS	+	Single	Glans penis
29	Father	26	Mefenemic acid	+	Single	Trunk
	Son	10	Mefenemic acid	+	Single	Trunk
30	Father	40	Amoxycillin	+	Single	Face/trunk
	Daughter	17	Amoxycillin	+	Single	Face
31	Father	25	Paracetamol	+	Single	Lip
	Son	16	NSAIDS	+	Single	Trunk
32	Brother	19	Sulfa drugs	+	Single	Back
	Brother	32	Sulfa drugs	+	Single	Trunk

A genetic predisposition to drug hypersensitivity has been suggested in various studies; and most significant genetic associations have been identified in the major histocompatibility complex for drugs such as abacavir, carbamazapine and allopurinol. However, hypersensitivity in one population may not be relevant for another population.[2,30] On observing familial cases of fixed drug eruption, Pellicano et al conducted a study on 36 patients with FDE, the link with HLA-B22 and Cw1 antigens was determined.[30]

In the study by Hung et al in 2005, a strong association of the allele HLA-B*5801 with the susceptibility of allopurinol-induced HSS, SJS, and TEN in Han Chinese was identified. In fact, the association is 100% in that the HLA-B allele B*5801 was present in all 51 patients with allopurinol-induced SCAR. Other ethnic allopurinol–SCAR patients were not available for the study but it has been observed that HLA-B*5801 allele is also present in other populations (7% in Africa, ≈2–7% in Caucasian, and 8% in Asian Indian).[5]

The study conducted by Palikhe et al suggested genetic association with intolerance to aspirin. They proposed that the genetic markers for AIA include HLA- DPB1*0301, leucotriene C4 synthase (LTC4S), ALOX5, CYSLT, PGE2, TBXA2R, TBX21, MS4A2 together with the four- locus SNP set B2ADR 46A>G, CCR3−520T>G, CysLTR1−634C> T
and FCER1B−109T>C. HLA- DB1*0609, ALOX5, FC ER1A and HNMT have been identified for AIU.[3] Another study described three cases of intertriginous drug eruptions; two of whom developed flexural exanthematous rash and mild systemic symptoms following amoxicillin and one due to administration of celecoxib.[17]

Hung et al conducted a study on 91 patients to conclude that the cutaneous adverse reactions caused by anticonvulsant carbamazepine have a strong association with the HLA-B*1502 gene.[31] In a similar study by Ozeki et al, HLA-A*3101 allele was present in 60.7% patients with cutaneous adverse drug reactions; hence identifying the allele as a genetic risk factor for the same in Japanese population.[32]

Hughes et al identified association of genetic variations in major histocompatibility complex allele HLA-B*5701 with hypersensitivity to abacavir, an antiretroviral drug, in white males and females.[33,34] Kim et al also suggested that HLA-DRB1*1302, HLA-DQB1*0601 and HLA-DPB1*0201 may be strong genetic markers for aspirin induced urticaria/angioedema.[35] Roujeau et al, in their study, observed that sulphonamide-related cases of TEN were linked to A29, B12 and DR7 while oxicam related cases of TEN were linked to A2 and B12.[36]

Various studies have shown that cashew nut consumption by allergic patients can cause severe reactions.[10-14,37,38] It has been mentioned that the major cashew allergens are Ana o 1, Ana o 2 and Ana o 3. Ana o 1 is a 50kDa vicillin-like protein resistant to heat and proteolysis. Ana o 2 is a 33 kDa legume-like protein and Ana o 3 is a 13 kDa 2S albumin. All three allergens are classified as seed storage proteins. It has been documented that of patients allergic to cashew nut, 50% are sensitized to recombinant Ana o 1, 62% to recombinant Ana o 2 and 81% to recombinant Ana o 3 determined by Western immunoblotting.[7-9,39]

In different countries, there are different drugs causing FDE; e.g. In India, sulpha and aspirin have a major chunk followed by tetracyclines, phenylbutazoe, NSAIDS, ampicillin, amoxicillin and phenolphthalein in the earlier years of the study; being much less used nowadays. Also, a case of cashew nut sensitivity was seen only three years back because prior to that we never suspected fixed reaction to foods.

As the clinical spectrum is quite varied, the diagnosis of FDE is not as straightforward as generally thought. FDE often presents with a wide spectrum of clinical manifestations indistinguishable from those of other skin diseases, such as erythema multiforme[40], SJS or TEN, cellulitis[41], paronychia, neutrophilic dermatosis[42],

lichen planus and parapsoriasis en plaques[43]. Such unusual forms of FDE may be easily overlooked unless clinicians take special care to recognize the presence of such variants.[40] As blister formation often occurs at an advanced stage of FDE reactions in association with systemic symptoms such as fever, clinicians often find a great deal of difficulty in distinguishing between a multiple, bullous variant of FDE and TEN, particularly when bullous lesions become more widespread with systemic manifestations. In addition, this variant does not leave typical hyperpigmentation after clinical resolution as is typically seen in nonpigmenting FDE, thus often leading to misdiagnosis as TEN or bullous pemphigoid.[44] Careful history taking about drug intake and a prior history of recurrent lesions in the same sites are essential for the precise diagnosis of FDE.

Routine laboratory investigations are not diagnostic and other tests such as peripheral eosinophilia, in-vitro lymphocyte toxicity, intradermal and patch testing and and lymphocyte proliferation test have limited clinical use. The challenge tests too are open to misinterpretation.[45] Therefore the diagnosis is mainly on high clinical suspicion and is often an assessment of probability. Apart from this, an early clinical diagnosis and appropriate management which is withdrawl to the offending drug is of importance. Systemic oral challenge and topical provocation tests are usually performed to identify the drug responsible for the FDE.[1]

CONCLUSION

Our study also supports that a genetic predisposition does contribute to the familial pattern of adverse drug reactions. Even cashew nut allergen may be considered as a potent allergen, which may cause reaction of varied severity when ingested by sensitized individuals.We think that in the next decade or two when genetic studies may be available fully and cheaper in cost, then we might be able to find the exact gene responsible for causing FDE.

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