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Epidemiological and Evolutionary Aspects of Severe Toxidermia Seen in the Dermatology Department of the University Hospital Center Joseph Raseta Befelatanana of Antananarivo

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Abstract

Introduction: Serious toxidermia are acute idiosyncratic reactions, which are infrequent but may compromise the patient's vital prognosis in the medium term. The objective of our study was to report the epidemiological and clinical profile of the serious drug toxicidermies seen at the Department of Dermatology-University Hospital Center Joseph Raseta Befelatanana.

Methods and Patients: This is a retrospective, descriptive study in the Department of Dermatology-University Hospital Center Joseph Raseta Befelatanana, over a period of 24 months from May 2015 until April 2016.

Results: Forty-two cases of severe toxidermias were recorded during the study period with a frequency of 1.28%. The average age was 33.6 years with a sex ratio of 0.55. The clinical forms found in order of decreasing frequency were toxic epidermal necrolysis, drug hypersensitivity syndrome and erythroderma. Antiepileptic drugs, particularly Carbamazepine and Phenobarbital, were the most incriminated, accounting for 66.67% of cases. Anti-tuberculosis drugs were reported in 11.91% of cases and antibiotics in 9.52% of cases. Three cases of death had been recorded despite well-managed care in hospitals. Stopping the responsible medication is the cornerstone of treatment.

Conclusion: The regularization, the control, the limitation of abusive sales of the drugs with risks could contribute to reduce the incidence of this pathology endowed with a still non-negligible mortality.

Keywords: *Toxidermie; Severe; Drugs; Antananarivo*

Introduction

Toxidermia are cutaneous side effects of a systemically administered drug [1]. They are among the most frequently reported adverse drug reactions at the pharmacovigilance center worldwide [2]. They can be isolated or associated with systemic manifestations, hence its severity [1]. Serious toxidermia are acute idiosyncratic reactions. The basic analysis of the data of the national pharmacovigilance center in Madagascar, between January 2013 and December 2014, shows that the toxidermia represent 38,40% in 2013 and 42,61% in 2014 of all the registered medical conditions of origin [3-6]. Recent data on severe forms requiring hospital management because they may involve the patient's vital prognosis in the medium term are still poorly estimated. Our objective is to describe the epidemiological and clinical evolution of the cases of serious toxicidermies hospitalized with the USFR Dermatology of the CHUJRB.

Methods

This is a monocentric, retrospective, descriptive study performed in the Dermatology Department of the Joseph Raseta Befelatanana Hospital of the University Hospital of Antananarivo concerning patient records that developed severe toxidermia over a period of 24 months ranging from May 2014 until April 2016. We included hospitalized patients with rash connected to a context of severe toxidermia diagnosed by specialist dermatologists. Non-inclusion criteria were of interest to patients with benign toxidermia and patients with incomplete records were excluded. We analyzed for each patient demographic parameters such as age and gender; clinical parameters such as the type of medication (self-medication or prescription), the number of drugs consumed, the main drugs involved, the associated pathologies or comorbidities, the type of ttoxidermia, intercurrent complications, the duration of hospitalization and the evolution of the patient after treatment. The collections of the data were carried out by Excel 2010 software. The statistical analysis was processed on the software EPI-INFO version 3.5.3 year 2011 and the result was retained as significant with a value of p less than 0.05.

Results

The total number of forms of toxidermia was 69, of which 27 were benign forms. Forty-two cases of serious drug toxicity were identified in a sample of 3264 patients seen in the dermatology department, a proportion of 1.28%. The sex ratio was 0.55. The average age was 33.6 years with an extreme of 12 to 76 years. The majority of the medication that caused the rash was on prescription, 85.71%. It was self-medication in 6 cases, i.e. 14.29%. The number of medications consumed per patient ranged from 1 to 8 drugs (Table 1). Antiepileptic drugs were the most incriminated in 28 cases or 66.67%, particularly carbamazepine which was found 23 times or 54.76% (Table 2). Carbamazepine was significantly responsible for the onset of severe hypersensitivity syndrome (DRESS syndrome) and toxic epidermal necrolysis (TEN) with a p-value of 0,04225 (Table 3). Five clinical forms had been observed. TENs including Steven Johnson's syndrome and Lyell's syndrome were the most frequent involving 25 cases (59.53%) followed by the DRESS syndrome for 11 cases (26.19%), erythroderma in 3 cases (7,14%) and other clinical forms for the remaining 3 cases (7.14%). The other three clinical forms concerned 1 case of angioedema in a 26-year-old male, attributed to Diclofenac, and 2 cases of maculopapular exanthema with signs of severity such as drug-induced hepatitis and eosinophilia greater than 500/mm3 in a 24-year-old woman attributed to carbamazepine and another

68-year-old woman attributed to allopurinol. The co-morbidity study revealed that epilepsy was the main associated pathology, followed by arterial hypertension, pleuropulmonary tuberculosis, atopy and complicated diabetes with coronary heart disease of 40.48%, 16.67%, 11.91%, 4.76% and 2.38%. Nine patients or 21.42% had no pathology or associated tare. Therapeutically, stopping the drug in question was the first therapeutic step. The electro-electrolyte rebalancing associated with analgesia and local skin care was the therapeutic basis for all our patients. Systemic corticosteroid therapy of 0.5 to 1 mg/kg/day with progressive degeneration was reserved for cases of DRESS syndrome. More than half of our patients (61.89%) had complications that were secondary to superinfection of skin lesions in 38.09% of cases (Table 4). Healing was observed in 37 patients (88.09%) and 3 patients (7.14%) had died. The cause of death was fulminant hepatitis in two patients on antituberculosis drugs and severe hepatocellular insufficiency in a patient on carbamazepine. One case of TEN had been transferred to the intensive care unit for better management and 1 case of erythroderma had come out of the hospital against medical advice. The average duration of hospitalization was 10.21 days with an extreme of 5 and 31 days.

Number of medications	Effective n = 42	Percentage (%)
One drug	15	35,71
Two medications	13	30,95
Three Medications	6	14,28
Four Medications	3	7,14
Five Medications	3	7,14
> Five drugs	2	4,76

Table 1: *Distribution according to the number of medications consumed before the rash.*

Drugs	Frequency n = 42	Percentage %
Amoxicillin	2	4,76
Diclofenac	2	4,76
Ciprofloxacin	1	2,38
Carbamazepine	23	54,76
Phenobarbital	5	11,91
Allopurinol	1	2,38
Ampicillin	1	2,38
TB	5	11,91
Quinine	2	4,76

Table 2: *Distribution according to the drugs implicated.*

Types of serious drug eruptions											
Drugs	DRESS		TEN		Erythroderma		Other		Total		P
	Effective n=11	%26,19	Effective 25	%59,52	Effective 3	%7,14	Effective 3	%7,14	Effective 42	%	
Amoxicillin	0	0	1	2,38	1	2,38	0	0	2	4,76	0,04225
Diclofenac	0	0	1	2,38	0	0	1	2,38	2	4,76	
Ciprofloxacin	0	0	1	2,38	0	0	0	0	1	2,38	
Carbamazepine	6	14,28	16	38,09	0	0	1	2,38	23	54,76	
Phenobarbital	2	4,76	2	4,76	1	2,38	0	0	5	11,9	
Allopurinol	0	0	0	0	0	0	1	2,38	1	2,38	
Ampicillin	1	2,38	0	0	0	0	0	0	1	2,38	
Tb	2	4,76	2	4,76	1	2,38	0	0	5	11,9	
Quinine	0	0	2	4,76	0	0	0	0	2	4,76	

Table 3: *Relation Between drug offenders and toxidermia.*

No Complications	Frequency n = 42	Percentage %
Absence	16	38,09%
Drug hepatitis	2	4,76%
Fulminant Hepatitis	2	4,76%
Hepato-Cellular deficiency	1	2,38%
Metabolic acidosis	1	2,38%
Overinfection of skin lesions	16	38,09%
Pneumonia	2	4,76%
Urinary Tract Infection	2	4,76%

Table 4: *Distribution according to the complications found.*

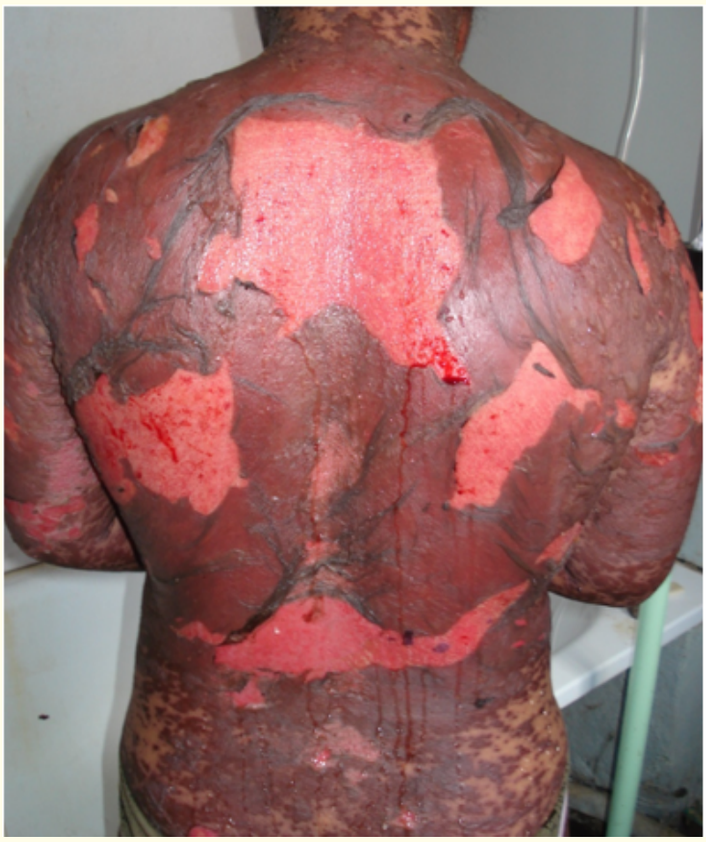

Figure 1: *A case of Lyell syndrome with epidermal detachments in wet clothes.*
(USFR Dermatology Archive Joseph Raseta Befelatanana University Hospital Center, Antananarivo, Madagascar).

Discussion

The frequency of severe 1.28% of cases of toxidermia that we observed in this study is similar to that found in literature with hospital prevalences ranging from 0.4% [3] to 1.53% [4]. The sex ratio was 0.55. This figure is comparable to that of Mrini LH., et al. [5] who found a female predominance of 64.3% on the same sample of 42 patients. The role of the genus in the development of cutaneous drug reactions is not fully clarified. The difference in pharmacokinetics, hormonal factors and the tendency of women to consume more drugs, especially through self-medication, and to consult more frequently than men, are clearly identified factors. In addition, reduced hepatic clearance in women also plays a role in this difference between the two sexes [6,7]. In our series, unlike the one described in the European literature, which emphasizes a high frequency in the elderly, serious toxidermia was of interest to young people with an average age of around thirty.

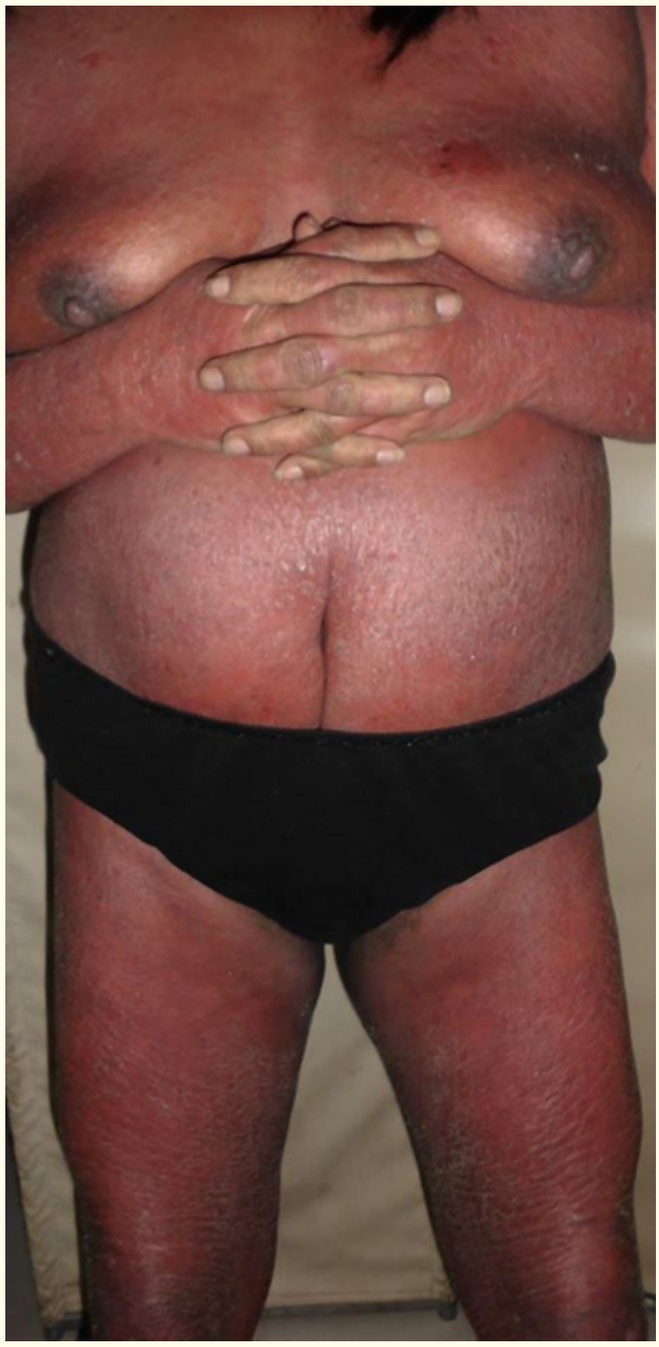

Figure 2: *A case of erythroderma.*

(Archives of the USFR de Dermatology Center Hospitalier Universitaire Joseph Raseta Befelatanana, Antananarivo, Madagascar).

This discrepancy is explained by their longevity but also because of the high incidence of polypharmacy in the elderly [8]. The majority of the medication that caused the rash was on medical prescription and self-medication was found only in 14.29% of cases. However, in some developing countries, as in the case of Mali, which is 51% in the Konare HD study, self-medication has become a common practice [9]. More than half or about 63% of our patients had at least one dual therapy. In the series published by Aguemon in 2006 on the Lyell syndrome in intensive care, the number of drugs consumed had an impact on the risk of this type of toxidermia [10]. As in the results observed by the authors before, it was the antiepileptics, the antibiotics represented by anti-tuberculosis drugs in our study, the nonsteroidal anti-inflammatory drugs which were the most incriminated [11,12] and that carbamazepine significantly favored the appearance of DRESS syndrome and TEN [13].

Regarding the comorbidities factors, our results had some similarities with those of Morocco reporting cases of serious toxidermia, of which epilepsy was also the main associated pathology, followed by atopy and arterial hypertension [14]. Note that given the significant prevalence of tuberculosis in Madagascar, which according to the WHO in 2014, was 406 per 100,000 inhabitants [15]. Five patients (11.91%) in our sample had pleuro-pulmonary tuberculosis associated with toxidermy. Clinically, similar to those observed by Kouassi., *et al.* [16], Raberahona., *et al*. [17], Mrini., *et al*. [5] TEN and DRESS syndrome were by far the most common clinical forms. From the therapeutic point of view, apart from the symptomatic conditioning that had benefited all our patients, only cases of DRESS syndrome had benefited from a systemic corticosteroid treatment. Despite the absence of randomized studies proving the effectiveness of the general steroids, this treatment is very used by several authors who agree to recognize him an efficiency controlling the evolution of the toxidermies, by reducing the fever and the sequels at the level visceral mucosa [18]. On the other hand, the efficacy of intravenous immunoglobulins still not available in our department, especially in the treatment of TEN and DRESS syndrome had been demonstrated [19,20]. The evolution of the disease was favorable despite the occurrence of intercurrent complications for most of our patients in 83% of the cases against 70% for Mrini., *et al.* [5] except the three deceased cases, the case transferred to intensive care and the case exit against medical advice.

Among the reported intercurrent complications, the rate of superinfection of mucocutaneous lesions is higher compared to the literature [5]. The duration of hospitalization depends not only on the type of complication but also and especially on the clinical form. In our study, mean hospital stay was 10.2 days versus 15.6 days for Saka., *et al* [20]. The limit of our study came from its monocentric type and the small size of the sample. Thus our results were only the reflection but did not represent all the cases of serious toxidermia existing in Madagascar

Conclusion

Although our results are not representative of all cases of serious toxidermia in our country, they could still serve as a tool to educate practitioners about the severity of these toxidermias and the importance of their notification. It should be noted that certain drugs in question were easily accessible to the public even without a medical prescription. However, given the extent of the involvement of these drugs in the development of serious toxidermia, the competent authorities should review their marketing authorization (MA) and encourage health personnel to inform patients when prescribing high-risk drugs such as antiepileptics and antibiotics.

Contributors of the Authors

Ranaivo Irina Mamisoa, Sendrasoa Fandresena Arilalala, Harioly Nirina Marie Osé Judicael has contributed to the manuscript meeting.

Raharolahy Onivola, Andriamanantsara Lovatiana Lahaina, Andrianarison Malalaniaina has contributed to the collection of data and search of bibliography.

Ramarozatovo Lala Soavina has contributed to the mime and form and correction of the manuscript.

Rapelanoro Rabenja Fahafahantsoa supervised the work of the work and contributed to the final manuscript correction.

All the authors have read and approved the final version of the manuscript.

Conflicts of Interest

None.

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