

Toxic Epidermal Necrolysis in Senegal, 2005 Through 2015: Epidemiological and Drug Etiology

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Abstract

Introduction: The aim of this study was to determine the epidemiological and drug etiology of the toxic epidermal necrosis (TEN) or Lyell's syndrome in our Department.

Patients and Methodology: Medical records of all admitted patients for TEN over an eleven-year period were analysed retrospectively.

Findings: We collected 251 cases of drug-induced skin reactions, representing 0.3% of medical visits and 0.7% of admissions. On average, 5 patients suffering from TEN were hospitalized every year. They mostly consisted of young women with a mean age of 35 ± 19.71 years and a sex-ratio of 0.5. About half of patients have been evacuated by road from the various provinces of the country, sometimes over 500 km away. The culprit drug was prescribed by a nurse of an infirmary in 35% of the cases. A self-medication with a drug bought in the street or in a pharmacy was found in 24 patients (40%). There was poly-medication in 17 patients (28%). The inducing drugs were mostly sulphonamides, neuroleptics, paracetamol, allopurinol and NSAI. An oral phytotherapy (Momordica charantia and Guiera senegalensis) induced the TEN in 2 patients. Death occurred in 18 patients (30%).

Discussion: Lyell syndrome is still frequent in sub-Saharan Africa where its prevalence even seems to be increased. Its incidence is probably favoured by self-medication especially with street medicines, unregulated access to drugs, inappropriate prescriptions, the circulation of counterfeit medicines, as well as the high prevalence of HIV. The remoteness of patients from dermatological department and the lack of sanitary evacuation systems explain its still poor prognosis in our regions.

Keywords: Drug-induced skin reactions; Lyell syndrome; Sub-Saharan Africa

Introduction

Over the last few years, several studies have been carried out on the Lyell syndrome or Toxic Epidermal Necrolysis (TEN) in sub-Saharan Africa [1-6]. It appears that this disease's prevalence is still higher in this region compared to the West [7-10]. Furthermore, its incidence also seems to increase in that region [6]. However, the key factors of this prevalence have not yet been fully characterized in these countries. The objective of this study was to determine the epidemiological and etiological characteristics of TEN in our department.

Patients and Methodology

We analysed retrospectively all medical records of patients hospitalized for TEN over an eleven-year period (2005-2015). In our country, almost all the patients with TEN were admitted in the Dermatology ward of the tertiary care hospital in Dakar.

The diagnosis of TEN was made based on the existence of an epidermal detachment higher than 30% with Nicholsky sign, associated with one or several mucous membrane involvement and systemic symptoms and on the histological findings. The culprit drug was determined based on careful analysis of the complete medication history over the previous 2 months with comparison with the literature data and online databases and on the French pharmacovigilance criteria for causality assessment [11]. The data were collected using Sphinx V5 and analysed with Epi Info 7.

Results

We collected 251 cases of Adverse Cutaneous Drug Reactions (ACDR), corresponding to a frequency of 23 cases every year and representing 0.3% of the medical visits and 0.7% of admissions over the

same period. The mean age of patients was 40 years ± 21.0 (ranged from 1 to 90 years). There were 163 women with a sex-ratio (M/F) of 0.5.

Among patients hospitalized for ACDR, the commonest reaction pattern observed was SJS- TEN spectrum of illness (121 cases; 48.2%). This spectrum consisted of 34 cases of Steven Johnson syndrome (SJS), 27 cases of SJS/TEN overlap syndrome and 60 cases of TEN (24%) (Figure 1). On average, 5 cases of TEN (Lyell syndrome) were registered every year. The mean age of patients with TEN was 35 ± 19.71 years {extremes 1 and 80 years} with a sex-ratio of 0.5. The TEN had mostly occurred (65%) in young subjects (16-60 years) and rarely among infants (12 cases; 20%) or elderly subjects (9 cases; 15%). About half of patients (41.7%) came from the various provinces of the country, located sometimes over 500 km away.

The TEN occurred in 3 pregnant patients and in 34 patients with a chronic disease (HBP, metabolic, autoimmune, infectious, atopic, hematological or neurological disease) including 3 HIV- positive patients. Only 2 patients had a previously known allergy to sulfonamides and paracetamol. No family history of drug allergy had been found.

The causative drug of the TEN was prescribed by a nurse of an

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infirmery in 21 cases (35%). A self-medication with a drug bought in the street or at a drugstore was found in 24 patients (40%). There was a poly-medication in 17 patients (28%).

The identified offending drugs are mentioned in Figure 2. The sulfonamides were represented by the trimethoprim sulfamethoxazole (8 cases) and the pyrimethamine sulfadoxine (4 cases). The neuroleptics consisted of phenobarbital (5 cases) and carbamazepine (3 cases). An oral phytotherapy (*Momordica charantia* and *Guiera senegalensis*) was responsible of the TEN in 2 patients. After an exhaustive etiological screening, the causative drug of the TEN could not be determined in 13 cases.

The mean duration before admission was 14 days and 3 weeks for 15 patients (25%). The body surface involved was higher than 50% among 40% of the patients (Figure 3). The mucosal involvement observed in all patients, affected the mouth in 54 patients (90%), the conjunctiva in 48 patients (80%) and the genitalia in 36 patients (60%).

At admission, there were hydroelectrolytic disorders (27 cases; 45%), infections (23 cases; 38.3%), cardiovascular collapse (9 cases; 15%) hepatic cytolysis (6 cases; 10%) and renal failure (5 cases; 8%). Infections were bacterial (17 cases) especially with Gram negative bacillus and viral (5 cases of herpes virus infection). The average duration of admission was 23 days.

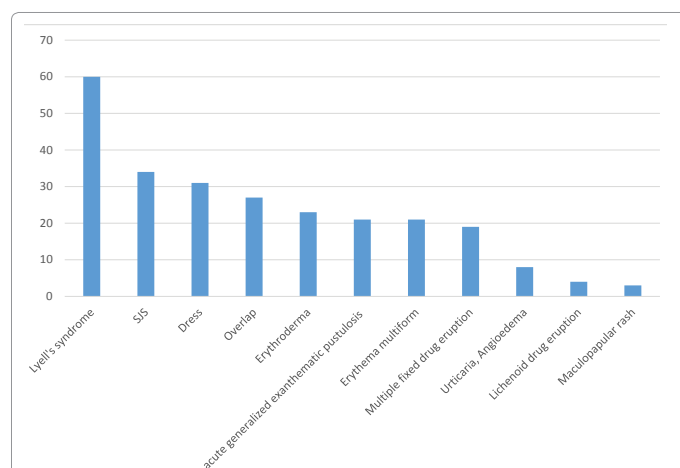


Figure 1: Distribution of different forms of cutaneous adverse reactions among admitted patients.

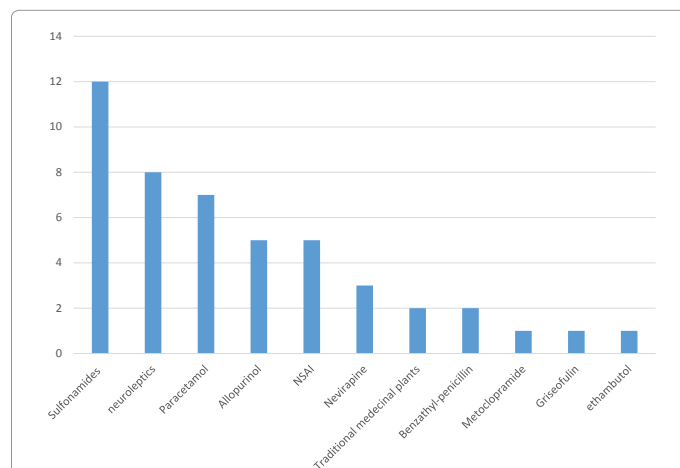


Figure 2: Distribution of molecules inducing Lyell syndrome.



Figure 3: TEN with necrotic epidermal detachment over 80% of body surface.®

All the patients were admitted in the Dermatology ward and non-essential medications were stopped upon arrival. They received supportive and symptomatic treatments with meticulous skin and mucous membrane care. No specific treatment was given.

The death occurred in 18 patients (30%), resulting from sepsis (9 cases), a cardiovascular collapse (4 cases), organ failure secondary to an underlying disease (3 cases), respiratory distress (1 case) and from pulmonary embolism (1 case).

Among the recovered patients, sequelae were noted on the skin (pigmentation, xerosis, hypertrophic scars: 29 cases), ocular (symblepharon, madarosis, corneal ulcer, keratitis, corneal pannus: 9 cases) and buccal (sudden loss of teeth: 1 case).

Discussion

In developed countries, TEN is a rare disease with an incidence of about 1 case per million inhabitants per year [7,9,10,12]. In Europe, TEN and SJS joint incidence is 2 cases per million inhabitants per year [13]. In Asia, it is estimated at 1.4 cases per million inhabitants per year [14]. TEN incidences in our study was 5 cases/year similar to the ones reported in several other series in sub-Saharan Africa [2,5]. A multicentric study comprising several West African francophone countries objectified a similar incidence of 4 cases/ year and per country [1]. Furthermore, compared to the previous studies carried out in our department and in the sub-region, we have noted an increased incidence of TEN [3,4,6]. This high incidence of ACDR and notably that of the Lyell syndrome in our regions compared to the West might partly be explained by self-medication, especially with drugs bought in the street, poly-medication, the circulating counterfeit drugs, phytotherapy, as well as the high rate of HIV prevalence [1]. Indeed, self-medication found in 25% of our patients is a frequent practice in our regions. It is due to an easy access, without medical prescription to medicines that are sometimes on free sale in the street, without appropriate conservation measures (Figure 4). In addition to that, such drugs are often counterfeit. The shortage of physicians and the high cost of medical care explain also the frequent and often inadequate prescribing practice by nurses in infirmaries.

Among ACDR, TEN was the most frequent in our study. This is certainly due to a recruitment bias, as the study population was comprised of inpatients with mostly severe ACDR referred in a tertiary referral centre.

TEN can occur at any age, but seems more frequent among the older subjects, due probably to a higher intake of drugs [6-8,12,13,15]. Like in



Figure 4: Free sale in the street of counterfeit drugs without appropriate conservation measures.

| | Senegal | Tunisia [16] | Togo [3] | Conakryl [2] | Cotonou [4] | Abidjan [5] |
|------------------------|---------------|--------------|---------------|---------------|---------------|---------------|
| Variables | (2005-2015) | (2001-2009) | (1992-2001) | (2000-2010) | (1998-2002) | (2000-2010) |
| | 11 years | 9 years | 10 years | 10 years | 5 years | 10 years |
| Number of cases | 60 | 18 | 12 | 28 | 14 | 50 |
| Hospital Frequency (%) | 0.12 | 0.95 | - | - | 0.25 | - |
| Sex ratio | 0.5 | 1.57 | 1.5 | 0.61 | - | 0.6 |
| Mean age (years) | 35 | 49 | 30 | 29.9 | 20.5 | 31.8 |
| Rate of deaths (%) | 30 | 41.21 | 41.7 | 35.7 | 28.5 | 46 |
| Most culprit drug | Sulfon-amides | Allopuri-nol | Sulfon-amides | Sulfon-amides | Sulfon-amides | Sulfon-amides |

Table 1: Comparative table of data on Project TEN in Africa.



Figure 5: Patients admitted in collective dermatological ward without isolation measures.

most studies in sub-Saharan Africa, TEN was mainly observed among the young in our study (mean age: 35 years) (Table 1) [1,3,5]. The female dominance in ACDR found in our study is widely reported [10].

In our country, only the capital city has dermatological departments. Remoteness of patients and the lack of a medical evacuation system explain the long delays before admission as well as the frequent complications, especially hydro electrolytic and infectious.

Like in almost all African series, the antibacterial sulfonamides were mostly in cause in the occurrence of the TEN in our study [2-5,16]. There are, of course often of allergenic nature, but this is also favored by the frequent and extensive prescribing practice of nurses.

Same reasoning applies to the causative agent benzathyl penicillin, which is used to treat all sorts of skin diseases. Moreover, pyrimethamin sulfadoxin is still systematically given to pregnant women for malaria prevention. Likewise, phenobarbital also a frequent trigger of ACDR is yet still widely used in our countries because of its low cost, instead of new generation neuroleptics. A genetic predisposition in this population might predispose to ACDR to that molecule [17].

In Western countries, paracetamol is rarely responsible for ACDR [18]. Its frequent responsibility in our study might be due to overconsumption of numerous counterfeit generic of this molecule, freely sold to people in the street for all kinds of symptoms. ACDR to Nevirapine is also frequent in Africa [1].

In 3 of our patients, the TEN was induced by a traditional medicinal plant. Their responsibility in the occurrence of ACDR is increasingly reported in our regions [19,20].

Despite the long delays before admission and the poor conditions of care (hospitalization in collective wards, lack of isolation measures (Figure 5), and the death rate was 30%, similarly to the rate recorded in Western countries [21]. This might partly be explained by the young age of occurrence of TEN in our patients.

Conclusion

Lyell syndrome is still frequent in sub-Saharan Africa where its prevalence seems moreover to be increasing. It is mostly observed among the younger subjects. Its frequency is probably favoured by self-medication especially with street medicines, unregulated access to medicines, unsuitable prescriptions, the circulation of counterfeit drugs, as well as the high prevalence of HIV infection. The remoteness of patients from dermatological units and the lack of medical evacuation systems explain its still poor prognosis in our regions.

Conflict of Interests

None

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