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## Letter to the Editor

### Cutaneous adverse drug reactions in pediatric patients: A moroccan multicenter study

*Les toxidermies chez l'enfant: une étude marocaine multicentrique*

#### 1. Introduction

Adverse drug reactions (ADRs) are defined as any harmful or unintended reactions to a drug that occur at doses used for the prevention, diagnosis or treatment of a disease [1].

Such reactions are normally classified as type A and B. Type A reactions are predictable and are usually dose-dependent and related to the known pharmacological action of the drug. Type B reactions are unpredictable and are not dose-dependent. This group includes cutaneous hypersensitivity drug reactions [2]. In children, ADRs represent a diagnostic challenge. On the one hand, children are more susceptible than adults to drug-dosage errors because of their smaller body size, and on the other, ADRs can mimic other skin diseases of children, especially viral exanthema, frequently appearing as a maculopapular or morbilliform rash sometimes indistinguishable from cutaneous drug reactions (CDR) [3,4].

##### 1.1. Aim

In this study, we present an analysis of CDR reports involving pediatric patients (18 years or younger) to study the epidemiological, clinical, etiological and evolutionary aspects of the various forms of CDR.

#### 2. Materials and methods

Multicentric retrospective study at the department of dermatology, pediatrics, pediatric intensive care and the pharmacovigilance department at the Ibn Rochd University Hospital in Casablanca from January 2011 until October 2018. Patients to whom no medication was given, those aged over 18 years, and patients with eruptions consistent with viral exanthema were excluded from the study. Data collected on patients consisted of age, sex, implicated drugs, indication of use, time of onset, type of skin eruption, distribution and duration of rash, previous experience with the drug, presence of interacting diseases, other drugs or clinical conditions, and laboratory results. Diagnosis was based on clinical history of reactions, physical examination, laboratory findings (including complete blood count and serum IgE level), and skin biopsy if needed. Diagnosis was made based on the criteria of drug imputability set out in the French method developed by Begaud et al. [5].

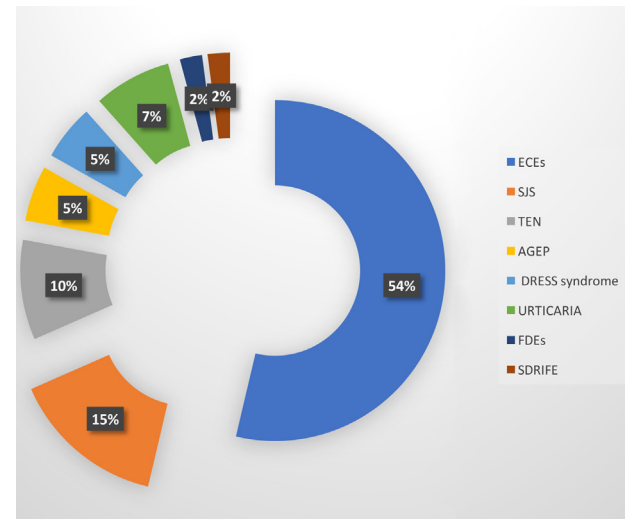


Fig. 1. Types of cutaneous drug reactions.

#### 3. Results

At the end of the study period and after applying the exclusion criteria, 89 children with CDR were identified, comprising 45 males and 44 females. The mean patient age was 1.02 years (range: 4 months to 18 years). The onset of clinical signs varied according to type of CDR. Clinical presentation consisted of exanthematous cutaneous eruptions (ECEs) in 46 cases (51%), Stevens Johnson syndrome (SJS) in 12 cases (14%), toxic epidermal necrolysis (TEN) in 8 cases (9%), urticaria in 6 cases (7%), acute generalized exanthematous pustulosis (AGEP) in 5 cases (5%), drug rash with eosinophilia and systemic symptoms (DRESS) in 5 cases (5%), fixed drug eruption (FDE) in 1 case (2%), symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) in 1 case (2%), and other types of CDR in 5 cases (5%) (Fig. 1).

ECEs, SJS, TEN and urticaria were the most common CDR, and the most common responsible drugs were antimicrobials, non-steroidal anti-inflammatory drugs (NSAIDs) and chemotherapy drugs (Table 1).

Skin biopsy (punch biopsy from the lesion area) was performed before treatment in 10 patients (3 DRESS, 3 SJS and 4 TEN) and showed the presence of eosinophils, edema, inflammation, vasculitis and necrotic changes.

The responsible drugs were systematically discontinued in all patients. Symptomatic treatment was required in all cases. Two cases of DRESS required the use of systemic corticosteroids. Complications consisted mainly of electrolyte disturbance in 12 cases (31.76%), acute renal failure in 6 cases (18.82%) and sepsis in 3 cases (7.9%). No fatalities were reported.

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**Table 1**  
Forms of cutaneous adverse drug reactions and causative agents.

|           | Antibiotics | Anti-convulsivants | NDAIS | Chemotherapy Drug | Others | Total |
|-----------|-------------|--------------------|-------|-------------------|--------|-------|
| ECEs      | 29          | 4                  | 3     | 7                 | 3      | 46    |
| SJS       | 2           | 3                  | 4     | 1                 | 2      | 12    |
| TEN       | 2           | 2                  | 3     | 0                 | 1      | 8     |
| DRESS     | 0           | 4                  | 0     | 0                 | 0      | 4     |
| AGEP      | 3           | 0                  | 0     | 0                 | 1      | 4     |
| URTICARIA | 5           | 0                  | 0     | 1                 | 0      | 6     |
| FDEs      | 0           | 0                  | 2     | 0                 | 0      | 2     |
| SDRIFE    | 0           | 0                  | 2     | 0                 | 1      | 3     |
| Others    | 1           | 0                  | 3     | 0                 | 0      | 4     |

#### 4. Discussion

CDRs account for a large proportion of ADRs, which constitute an extensive medical and public health problem among children. In both children adults, most epidemiologic studies usually include both types, with marked predominance of type A reactions. The reported incidence of ADRs in the pediatric population is generally considered lower than in adults. Nevertheless, a recent systematic review of the published data for children showed that 0.4% to 10.3% of all pediatric hospital admissions may be ADR-related (2.9% overall incidence) and that 0.6% to 16.8% of all children exposed to a drug during a hospital stay may present an ADR [6].

Analysis of submissions to the World Health Organization ADR VigiBase showed that CDR accounted for 35% of all suspected ADRs in children [4]. Canadian reports submitted from 2005 to 2008 demonstrated that 16% of all ADRs in children were cutaneous, 66% of them serious, and that the majority could be attributed to antimicrobial and antiepileptic drugs [7].

According to studies conducted in outpatients, it is estimated that 2.5% of children treated with a drug, and up to 12% of children treated with an antibiotic, will experience a CDR. (8) The skin is the organ most frequently affected by drug-induced allergic reactions. Various genetic and environmental factors may predispose subjects to such reactions and at least 29 drug-related cutaneous reaction patterns have been reported [2,8–12].

Depending on the time from the last drug administration to onset, drug hypersensitivity reactions can be classified as either immediate (onset within 1 h) or non-immediate (> 1 h to onset). Type-I (IgE-mediated) and type-IV (T cell-mediated) pathogenic mechanisms are involved in most immediate and non-immediate reactions, respectively. Immediate reactions usually present clinically as urticaria, angioedema, rhinitis, bronchospasm and anaphylactic shock. In many non-immediate ECEs a genetic predisposition has been demonstrated. The pharmacogenetics of these reactions is currently being investigated, with promising results in the screening of patients before administration of medications carrying a high risk for severe ADRs [13].

At least 29 drug-related cutaneous reaction patterns have been identified [14]. The 5 most common reactions described in the pediatric population are ECEs, urticaria, FDEs, photosensitivity reactions and serum sickness-like reaction.

ECEs are the most common drug-induced eruptions [15]. The incidence of such reactions is increased in the presence of viral infections (Epstein–Barr virus, HIV infection). The most common classes of drugs implicated include penicillin, sulfonamides, cephalosporins and antiepileptic medications [16]. ECEs are characterized by erythematous macules and/or papules, usually beginning 7–14 days after the initiation of a new medication, and sometimes after drug discontinuation. The eruption is usually symmetrical, beginning on the trunk and becoming generalized, and without blistering or pustulation. Mucous membranes are usually spared, but palms and soles are often involved. Pruritus is the

main symptom. The eruption is generally self-limiting and often turns brownish-red before fading within 7–14 days of discontinuation of the offending drug. Scaling or desquamation may follow. Re-challenge may lead to reactions within a few days.

Urticaria is a common disorder in children and adults and usually signals a type 1 (or immediate) hypersensitivity reaction. This involves a protein or its metabolite binding to IgE on the surface of cutaneous mast cells, leading to activation, degranulation, and release of vasoactive mediators, e.g. histamine, leukotrienes and prostaglandins. Urticaria may also result from non-immunologic triggering of mast cell release, e.g. radiocontrast media, aspirin, NSAIDs and opioids. In children, the main cause of urticaria is infection. In our study, urticaria was caused primarily by antibiotics.

The incidence of drug reactions is 6.1% in hospitalized patients, with 41.4% of these being classified as serious drug reactions and 1.2% resulting in death [17].

Severe CDR are rare but are potentially associated with morbidity and mortality, and they must thus be treated early and appropriately. These severe CDR include DRESS, SJS, TEN and AGEP. In our study, severe CDR accounted for 33% of all CDR with the most widely incriminated drugs being anti-convulsants. In severe CDR many organs may be affected, including liver, kidney, heart, lung, brain, thyroid and pancreas. Visceral involvement often determines severity. The liver is reported to be the most frequently affected organ (60%–80%), and renal failure is seen in 10% to 30% of cases. In our study, the kidney was the most frequently affected organ, being seen in 6 patients, with electrolyte disturbance being noted in 12 cases and sepsis in 3 cases.

Antibiotics were the most common cause of CDR (47%) in this study, followed by NSAIDs (19%), anticonvulsants (15%) and chemotherapy drugs (10%) (Table 1).

The results of our study were compared with other African series (Table 2). In the Turkey and Guinea series, there was a clear predominance of severe CDR compared to the Tunisian series and to our Moroccan study; this is due to a selection bias, with the Turkish and Guinea series being chiefly concerned with severe CDR, while our series as well as the Tunisian series included all cases of CDR.

Early pattern recognition and severity assessment of a CDR are the cornerstones of initial management and prevention of progression of the reaction. The main goal of treatment is discontinuation of the suspected drug, although this is not always possible. If a patient is on several medications, it may be difficult to identify exactly which is the causative drug. In such cases one might opt for sequential withdrawal considering the type of reaction, the temporal relation, and the frequency with which the drug has been associated with the patient's cutaneous reaction, always keeping in mind that the patient should be monitored closely [15].

Urticarial reactions and EMP can be managed only symptomatically to reduce skin inflammation and pruritus. For moderate to severe reactions, systemic corticosteroids can be helpful. In severe reactions, the treatment strategy should be adapted to the severity of visceral involvement. No clear therapeutic guidelines exist

**Table 2**

Table comparing the results of our study with other African series.

|                          | Our study | Tunisian study | Turkish study | Guinea study |
|--------------------------|-----------|----------------|---------------|--------------|
| Period of study          | 2011/2018 | 1991/2008      | 2011/2016     | 2000/2014    |
| Total number of patients | 89        | 90             | 58            | 35           |
| Sex                      | 44F/45H   | 49H/41F        | 29H/29F       | 18H/17F      |
| Age                      | 8.04      | 6.9            | 8.2           | 11.3         |
| Type of CADR             |           |                |               |              |
| EMP                      | 51%       | 57.7%          | –             | –            |
| SJS/Lyell                | 23%       | 10%            | 60.40%        | 68.50%       |
| URTICARIA                | 7%        | 16.60%         | –             | –            |
| AGEP                     | 5%        | –              | 12%           | 2.85%        |
| DRESS                    | 5%        | –              | 27.60%        | 2.85%        |
| Fixed pigmented erythema | 2%        | 14.40%         | –             | 22.85%       |
| SDRIFE                   | 3%        | –              | –             | –            |
| Others                   | 5%        | –              | –             | –            |
| Causative agents         |           |                |               |              |
| ATB                      | 47%       | 55.50%         | 51.70%        | 62.85%       |
| Anti inflammatory        | 19%       | 18.80%         | –             | 5.71%        |
| Anticonvulsants          | 15%       | 11.10%         | 31%           | –            |
| Chemotherapy drugS       | 10%       | –              | –             | –            |
| Paracetamol              | 4.50%     | –              | –             | –            |
| Antibacillary            | 2.20%     | –              | –             | –            |

regarding the use of medications for the treatment of SJS/TEN in children [15]. Patients should be transferred to a pediatric intensive care unit. Systemic corticosteroids, plasmapheresis, intravenous immunoglobulin (IVIG) and immunosuppressive agents have been reported as being effective, with no evidence favoring any of them in particular [18]. The use of cyclosporine based on the capacity of calcineurin inhibitors has been advocated to rapidly block the functions of cytotoxic T cells [19]. CDR in children on chemotherapy for cancer may pose considerable problems because the suspected drugs may be lifesaving and cannot be withdrawn. The goal in these cases is to keep the patient comfortable and treat the CDR while maintaining the medication, unless a severe or even fatal reaction occurs [20].

## 5. Conclusion

Since CDR are relatively rare, multicentric studies are required to obtain more data despite some problems in interpretation of this data. The current multicentric study is the largest study on children in our country and provides meaningful information about the cutaneous eruption patterns of commonly used drugs. ECEs due to antimicrobials are the most common drug-induced eruptions in children. Drug imputability must be based on solid arguments since EMP can mimic many other childhood eruptions, especially viral infections, and also because of the frequent prescription of antibiotics in pediatrics.

## Disclosure of interest

The authors declare that they have no competing interest.

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