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ORIGINAL ARTICLE

Severe Cutaneous Adverse Drug Reactions in Children: Epidemiological, Clinical and Etiological Aspects in Dermatology-Venereology Unit at National and Teaching Hospital of Cotonou

Effets Indésirables Cutanés Sévères Chez les Enfants: Aspects Épidémiologiques, Cliniques et Étiologiques de l'Unité de Dermatologie-Vénéréologie de l'Hôpital National et Universitaire de Cotonou

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ABSTRACT

BACKGROUND: The aim of this study was to describe the epidemiological, clinical and etiological aspects of severe cutaneous adverse drug reactions in children in dermatology-venereology unit at National and Teaching Hospital of Cotonou.

METHODS: A retrospective and descriptive study was carried out for 10 years in dermatology-venereology unit at the National and Teaching Hospital of Cotonou to document the epidemiological, clinical and etiological aspects of severe cutaneous adverse drug reactions in children. It included all children aged from 0 to 18 years with clinical diagnosis of severe cutaneous adverse drug reactions. Drug imputability was based on the criteria of the French pharmacovigilance group.

RESULTS: Severe cutaneous adverse drug reactions accounted for 47.3% of paediatric cases (35/74 cases). The mean age was 9.3 years ± 5.2. The sex-ratio was 1.1. Self-medication was noted in 76.5% of children, on the initiative of parents in 66.7% of cases. There were 51.4% cases of Steven Johnson syndrome, 22.8% cases of Lyell syndrome, 8.5% cases of generalized and bullous fixed drug eruption, 2.9% cases of acute generalized exanthematous pustulosis and erythrodermic maculo-papular rash. Drug combinations was noted in 20% of cases. Penicillins (26.5%), paracetamol and sulfonamides (16.3%) were the drugs frequently incriminated.

CONCLUSION: Steven Johnson syndrome and Lyell syndrome were the main severe cutaneous adverse drug reactions in children, mostly of school age. Penicillins, paracetamol and sulfonamides were the drugs frequently used and administered most often on self-medication. **WAJM 2022; 39(5): 538–542.**

Keywords: Severe cutaneous adverse drug reactions, Steven Johnson syndrome, Lyell syndrome, self-medication, sulfonamides, children, Benin.

RÉSUMÉ

INTRODUCTION: L'objectif de cette étude était de décrire les aspects épidémiologiques, cliniques et étiologiques des toxidermies graves chez les enfants en dermatologie à Cotonou.

METHODES: Une étude rétrospective et descriptive a été réalisée sur 10 ans dans le service de dermatologie du Centre National Hospitalier et Universitaire de Cotonou pour documenter les aspects épidémiologiques, cliniques et étiologiques des toxidermies graves chez les enfants. Étaient inclus tous les enfants âgés de 0-18 ans chez qui le diagnostic clinique de toxidermie grave a été retenu. L'imputabilité médicamenteuse était basée sur les critères du groupe français de pharmacovigilance.

RESULTATS: Les toxidermies graves représentaient 47,3% des cas pédiatriques (35/74 cas). L'âge moyen était de 9,3 ans ± 5,2. La sex-ratio H/F était de 1,1. Une automédication a été notée chez 76,5% des enfants, sur l'initiative des parents dans 66,7% des cas. Il y avait 51,4% de cas de syndrome de Steven Johnson, 22,8% de cas de syndrome de Lyell, 8,5% de cas d'érythème pigmenté fixe bulleux étendu, 2,9% de pustulose exanthématique aigüe généralisée et d'exanthème maculo-papuleux eìrythrodermique. Une polymédication a été notée dans 20% des cas. Les pénicillines (26,5%), le paracétamol et les sulfamides (16,3%) étaient les médicaments fréquemment incriminés.

CONCLUSION: Le syndrome de Steven Johnson et le syndrome de Lyell étaient les principales toxidermies graves chez les enfants, majoritairement en âge scolaire. Les pénicillines, le paracétamol et les sulfamides étaient les médicaments fréquemment incriminés et administrés le plus souvent en automédication. **WAJM 2022; 39(5): 538–542.**

Mots clés: Toxidermies graves, syndrome de Steven Johnson, syndrome de Lyell, automédication, sulfamides, enfants, Benin.

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Abbreviations: AGEP, Acute Generalized Exanthematous Pustulosis; **DRESS,** Drug Reaction with Eosinophilia and Systemic Symptoms; **EMPR,** Erythrodermic Maculopapular Rash; **GBFDE,** Generalized Bullous Fixed Drug Eruption; **SCAR,** Severe Cutaneous Adverse Drug Reactions; **SJS,** Steven Johnson Syndrome; **TEN,** Toxic Epidermal Necrolysis.

INTRODUCTION

Cutaneous adverse drug reactions are skin and mucous manifestations due to oral or systemic drug administration.[1,2] They are the most common side effects reported to pharmacovigilance centres in the world. It can be an unpredictable occurrence characterized by a wide variety of symptoms and patho-physiological features.[2]

Severe or critical forms are characterized by significant morbidity and mortality, due to acute skin failure, systemic damage and other sequelae.[2,4] These are mainly Steven Johnson syndrome (SJS), Lyell syndrome or toxic epidermal necrolysis (TEN), overlap syndrome, generalized bullous fixed drug eruption (GBFDE), drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, anaphylaxis, erythrodermic maculopapular rash (EMPR), and acute generalized exanthematous pustulosis (AGEP). Toxic drug risks in children have higher morbidity and mortality in severe forms.[5,6] However, they are rarely studied, hence the objective of this study was to describe the epidemiological, clinical and etiological aspects of severe cutaneous adverse drug reactions (SCAR) in children in Cotonou.

METHODS

The study was retrospective and descriptive over a period of 10 years, from July 2007 to July 2017. The records of children aged between 0–18 years who consulted at the dermatology-venereology unit of the National and Teaching Hospital (CNHU-HKM) of Cotonou and in whom the clinical diagnosis of SCAR had been retained were included. These were mainly SJS, TEN, DRESS syndrome, GBFDE, EMPR and AGEP.[2,4,6] We have not included the benign forms of cutaneous drug reactions which, unlike the severe forms, are not life-threatening, neither functional nor aesthetic.

The diagnosis of each form was retained by a senior dermatologist on the basis of epidemiological and clinical arguments. Drug imputability was based on the criteria of the French pharmaco-vigilance group. The incriminated drugs had documented extrinsic imputability with a notoriety at high risk of cutaneous adverse drug reaction and a plausible or very plausible intrinsic imputability.[7,8]

The variables studied were socio-demographic (age, sex), clinical (history, type of cutaneous adverse drug reaction) and etiological (the drug(s) involved, circumstances of drug use). These data were collected using a pre-established survey form, then entered and analyzed with the EPI-Info 7 software.

The study was approved by the department head on behalf of the institutional research and ethics committee.

RESULTS

Over the study period, 74 cases of paediatric cutaneous adverse drug reactions were identified, of which 35 were severe cases. SCAR accounted for 47.3% of the cases of paediatric cutaneous adverse drug reactions.

The mean age was 9.3 years ± 5.2 with a predominance of children aged between 7–12 years (14; 45.7%), followed by those aged between 0–6 years (12; 34.2%) and those aged between 13–18 years (9; 25.7%). The proportion of children aged 7–12 is 40% instead of 45.7%.

Two children were known to be Human Immunodeficiency Virus (HIV) positive. Self-medication was reported in 76.5% (n = 26) and was initiated in 65.3% of cases (n = 17) by the parents. The main reasons for taking medication were fever (13; 50%), malaria (3; 11.5%) and pain (2; 7.7%).

Almost all of the SCAR diagnosed were bullous (33; 94.3%) and distributed as follows: SSJ illustrated by Figure 1 (18; 51.4%), TEN on Figure 2 (8; 22.8%), overlap syndrome (4; 11.4%) and GBFDE (3; 8.6%). The different clinical forms are described in Table 1.

The drug classes involved were mainly antibiotics (23 times; 65.6%), analgesics/antipyretics (13 times; 37.1%) and antimalarial drugs (10 times; 28.5%). In 8.6% of the cases (n = 3), the culprit drug had not been found. Polymedication had been noted in one child out of five (n = 7). Penicillins (13; 26.5%), paracetamol and sulfonamides (8; 16.3%) were the drugs frequently incriminated as summarized in Figure 3.

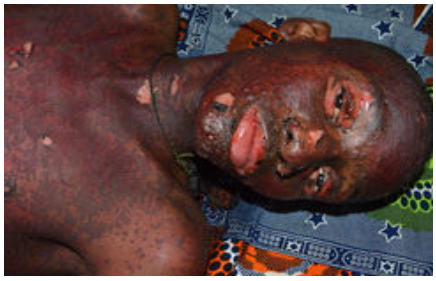

Fig. 1: Steven Johnson Syndrome in a Teenager with Bullous and Erosive Lesions of the Skin and Mucous Membranes.

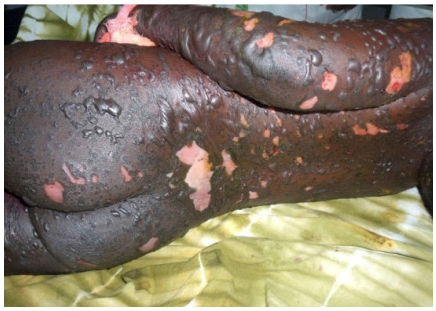

Fig. 2: Lyell Syndrome in a Child with Large Epidermal Detachments.

DISCUSSION

SCAR accounts for 2% of all cutaneous adverse drug reactions.[2,9] In children, the frequency is varied, estimated between 2–6.7%.[6] In our study, we identified 35 cases in 10 years, a frequency higher than that of Togo (14 cases in 15 years)[10] and that of Tunisia (09 cases in 18 years).[11] But when we compare the prevalence of pediatric SCAR in our study (47.3%) to the 20% reported by Adégbidi, *et al*[12] in the same department about a decade ago, we can state that in ten years it has doubled. This could be explained by the increased frequency of self-medication in Africa over the past 10 years.[1,10,12,13]

Both sexes are affected with a sex-ratio varying from 0.4 in Togo, 0.94 in Benin, 1.19 in Tunisie to 2 in a large French series;[5,10–12] in our series it was 1.1. The mean age of our series was 9.3 years ± 5.2, corresponding to the school period. This average is similar to that of Akakpo, *et al*[10] in Lomé who have noted a mean age of 10.9 years. Adégbidi, *et al* and Khaled, *et al*[11,12] found a lower mean age of 6.6 years and 6.9 years respectively.

Table 1: Clinical types of SCAR in Children in the Dermatology-Venerology unit from July 2007-July 2017 at National and Teaching Hospital of Cotonou

	Number	Percentage (%)
Steven Johnson syndrome (SSJ)	18	51.4
Lyell syndrome	08	22.8
Overlap syndrome	04	11.4
Generalized bullous fixed drug eruption	03	08.6
Acute and generalized exanthematous pustulosis	01	02.9
Erythrodermic maculo-papular rash	01	02.9
Total	**35**	**100.0**

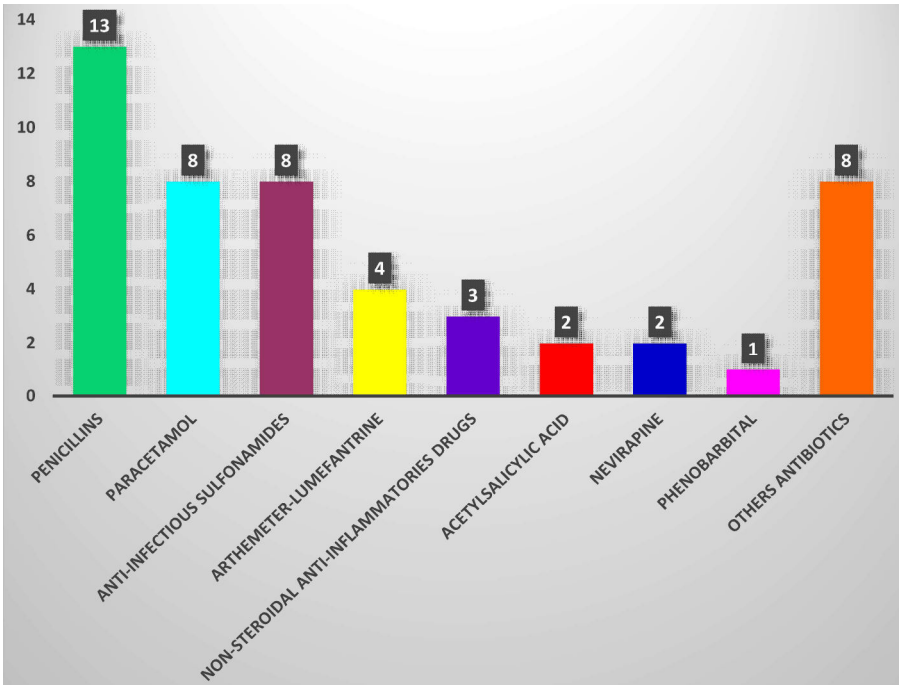

Fig. 3: Incriminated Drugs in the occurrence of Severe Cutaneous Adverse Drug Reactions in Children in the Dermatology-Venerology Unit at National and Teaching Hospital of Cotonou from July 2007 to July 2017.

Bullous cutaneous adverse drug reactions were in majority with 85.6% of epidermal necrosis (SJS-TEN). In sub-Saharan Africa, these two syndromes, combined within the same entity, hold the first place of severe cutaneous adverse drug reactions[1,10,12–16] and are characterized by extensive detachment of the epidermis and mucosal erosions. The distinction between SJS and TEN is based on the percentage of the body area affected (SJS = 10%; TEN = 30% and overlap syndrome 10–30%).[18] The time to onset is 4 to 28 days after the introduction of the culprit drug.[18,19] These severe forms of cutaneous adverse drug reactions may be accompanied by ocular complications and synechia.[6,10,14,16] The high mortality rate in our regions varies between 7.1–22.7%[1,10,13,15] and is mainly due to under-medicalization and particularly the lack of a referral centre or specialised intensive-care unit in the management of severe cutaneous adverse drug reactions.

Self-medication is the main favouring factor in our study (76.5%) as reported at variable rates in Ivory Coast,[1] Togo[10,13] and Benin.[12] This self-medication in sub-Saharan Africa could be explained by problems of geographical and economic availability, as well as the lack of health insurance. As the majority of patients are often in modest socio-economic conditions, in case of illness they resort to fake medicines that are sold illegally outside pharmacies and health care structures, as well as traditional therapeutics in the form of decoction-based drinks, which are of an imprecise nature.

Other contributing factors have been reported as child-specific factors,[5] the HLA system and some viral infections.[2,5,8,18] Because the child's body is immature, all the metabolisms of the drug (resorption, bioavailability, elimination) are modified compared to those of adults. Therefore, the metabolism of drugs administered, sometimes in overdose (administration of galenic forms unsuitable for children, especially in poor countries) is modified and can lead to the production and accumulation of toxic substances, which can induce cutaneous adverse drug reactions. The genetic abnormalities responsible for drug accidents involved in children are mainly enzymatic (depoxyde hydrolase deficiency).[5] Genetic work over the past decade has linked phenotypes of the major histocompatibility complex molecule to certain drugs in the SJS/TEN (HLA-B12 and TEN; HLA-B1502 and SSJ and TEN to carbamazepine; HLA-B5801 and severe reactions to allopurinol).[20] Similarly, some viral infections (HIV, Herpes simplex virus, Epstein Barr virus, Cytomegalovirus, mycoplasma, coxsackie) are a major risk factor for SCAR. Thus, during infectious mononucleosis the rate of amino-penicillin cutaneous adverse drug reactions can reach 90%.[5,6] Some studies have shown that taking paracetamol during *Herpes simplex virus* infections exposes to SCAR such as epidermal necrolysis, according to a European multi-centric study; which leads us to reconsider the alert issued by the Food and Drug Administration in 2013 regarding the responsibility of paracetamol in SCAR.[20]

The assessment of drug causality in a patient with cutaneous adverse drug reactions is referred to as imputability.[18] This approach, although probabilistic, requires a thorough investigation in search of all drugs taken on average in the 28 days before the first clinical signs.

It takes into account clinical presentation, accurate chronology of events and drug intake, and elimination of differential diagnoses.[7,8,21] In our study, the main drugs involved were penicillins 26.5% followed by paracetamol and anti-infectious sulfonamides (16.3%). These drugs are part of the therapeutic classes frequently used in paediatrics, but also those involved in pediatric cutaneous adverse drug reactions.[5,6,10,11,20]

The accountability of sulfonamides in the occurrence of cutaneous adverse drug reactions has been reported by several other African authors.[1,10,14,15] This high proportion of the anti-infectious sulfonamides involved in our regions is justified on the one hand by the widespread use, most often in self-medication, of the combination sulfadoxine-pyrimethamine for the treatment of endemic malaria in sub-Saharan Africa. On the other hand, the lower cost of sulfonamide antibiotics in our regions also explains the frequent use of this compound, most often as a self-medication, for any suspected symptoms of infection in children.

The simultaneous use of several drugs (estimated at 20% in our study) exposes to the risk of co-sensitization via "danger signals" or of innate poly-sensitization to viral replication. SCAR and non-steroidal anti-inflammatory drugs are believed to be contributing factors.[22,23]

A specific score was developed in the SJS/TEN, based on data from the EuroSCAR case-control study. This allows the identification of the drug involved in 70% of cases and eliminates the role of other drugs in 64% of cases. However, in about 5% of cases, no medication is found.[2] In our series, the absence of medication was observed in 8.6% of cases. A rate higher than ours of 23% was reported by Kourouma et al in Côte d'Ivoire.[1] Several hypotheses may explain the absence of medication intake found during our study. We can evoke the reliability of the parents' statements fearing guilt or forgetfulness, masked medicines, phytotherapy, which is not negligible in our regions and whose composition is often unknown. Some authors have reported an infectious etiology (viral infections, mycoplasma pneumonia) estimated between 25–30% of the series.[6,17,20] This finding could be explained by the interaction between certain infections and cutaneous adverse drugs reactions, which remains to be elucidated.

CONCLUSION

At the end of our study, we noted that SCAR, dominated by bullous forms, represented a significant proportion of paediatric cases in the Dermatology-venereology unit at National and Teaching Hospital in Cotonou. Self-medication was sometimes prominent in a context of combinations drugs.

Penicillins, paracetamol and anti-infectious sulfonamides were the main culprit drugs. A pharmacovigilance statement is essential in cases of SCAR, regardless of the medication involved.

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