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Brief Report

Cutaneous adverse reactions to antiepileptic drugs: 17 cases at the Dermatology Department of the Arrazi Hospital in Marrakech

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ABSTRACT

Background: Antiepileptics are among the drugs mainly implicated in cutaneous adverse drug reactions (CADRs). **Materials and Methods:** The aim of this case series was to study the epidemiological, clinical, evolutionary, and therapeutic profile of antiepileptic-drug-induced toxidermia and the most often incriminated antiepileptic drugs. **Results:** We collected seventeen cases of a CADR to antiepileptic drugs at the Dermatology Department of CHU Mohamed VI in Marrakech over a period of five years. The mean age was 42 years. The pattern of CADRs was as follows: DRESS syndrome in 52.9%, Stevens–Johnson syndrome in 23.5%, Lyell syndrome in 11.8%, and acute generalized exanthematous pustulosis and fixed bullous generalized drug eruption in 5.9% each. Carbamazepine was the most often incriminated antiepileptic drug. **Conclusion:** CADRs to antiepileptic drugs are dominated by DRESS syndrome. Through this study, we underline the potential of antiepileptic drugs to induce serious toxidermia and that, therefore, their prescription must be reasoned.

Key words: Cutaneous Adverse Reactions; Antiepileptics; Epidemiology; Prognosis; Pharmacovigilance

INTRODUCTION

Toxidermia is a group of cutaneous adverse reactions to drugs (CARDs) taken on medical prescription or self-medicated [1,2]. The severe and life-threatening conditions include anaphylaxis, acute generalized exanthematous pustulosis (AGEP), DRESS syndrome, Stevens–Johnson syndrome, and Lyell syndrome. These severe adverse reactions should be systematically reported to the pharmacovigilance authorities to allow for a better evaluation of the benefit-risk ratio of drugs. All drug classes may cause toxidermia, especially antibiotics, antiepileptics, and non-steroidal anti-inflammatory drugs. We conducted this case series to study the epidemiological, clinical, evolutionary, and therapeutic profile of toxidermia induced by antiepileptic drugs and to specify the most often incriminated antiepileptic drugs.

MATERIALS AND METHODS

The case series was conducted from January 2017 to December 2021 (for a period of five years) at a dermatology department in Marrakech on seventeen patients hospitalized for toxidermia to antiepileptics. Archival medical records were used to collect data. We began our study by elaborating on an exploitation form. The parameters submitted to the analysis were epidemiological, clinical, para-clinical, evolutionary, and therapeutic data. The results were recorded on a paper form, then entered into SPSS, version 20, and

How to cite this article: Amakha FZ, Khatem S, Aboudourib M, Hocar O, Zaoui S, Amal S. Cutaneous adverse reactions to antiepileptic drugs: 17 cases at the Dermatology Department of the Arrazi Hospital in Marrakech. Our Dermatol Online. 2023;14(3):283-286.

Submission: 11.01.2023; **Acceptance:** 23.03.2023

DOI: 10.7241/ourd.20233.9

were given in the form of percentages and numbers for the qualitative variables and in the form of averages for the quantitative variables. They were presented with histograms and tables.

RESULTS

Characteristics of the Patients

During the study period, a total of 87 patients were hospitalized at the Dermatology Department for toxidermia induced by different drug classes. Seventeen cases of toxidermia to antiepileptic drugs were reported during this period. The average age of the patients was 42 years, with extremes of 16 and 70 years. The most represented age group was between 16 and 52 years. There was a female predominance (82.4%). Epilepsy was the main indication for antiepileptic drugs in our study (8 cases; 47.1%), followed by psychosis (2 cases; 11.8%), depression (1 case; 5.9%), and post-herpetic neuralgia (1 case; 5.9%). The reason for prescription was unknown in 5 cases (29.3%). A history of toxidermia was noted in 11.8% (2 cases) of the patients. Five cases of toxidermia to antiepileptic drugs were noted during the year 2021 when compared to the years 2017, 2019, and 2020; four cases were found in each year, and no cases in 2018 (Fig. 1).

Pattern of Cutaneous Adverse Reactions Induced by Antiepileptic Drugs (Carads)

A total of seventeen different CARADs were observed. The most commonly observed CARADs were DRESS syndrome (Figs. 2a and 2b), Stevens–Johnson syndrome, and toxic epidermal necrolysis (Figs. 3a and 3b) (Table 1).

Cutaneous or general signs of severity were present in all patients. Purpura was observed in 23.5% (4 cases), confluent erythema in 29.4% (5 cases), facial edema in 47.1% (8 cases), mucosal erosions in 58.8% (10 cases), a positive Nikolsky's sign in 29.4% (5 cases), bullae in 5 cases, fever in 13 cases (76.5%), adenopathy and hypotension in one case, and arthralgia and respiratory distress in 2 cases. Pruritus was present in 82.4% (14 cases). Neurological signs associated with cutaneous side effects were represented by drowsiness in 3 cases (17.6%) and behavioral disorders in only one case (5.9%).

Causative Drugs

The common causative antiepileptic drugs were carbamazepine (52.9%), sodium valproate (23.5%), lamotrigine (11.8%), and phenobarbital (11.8%) (Table 2). All patients had received their medication

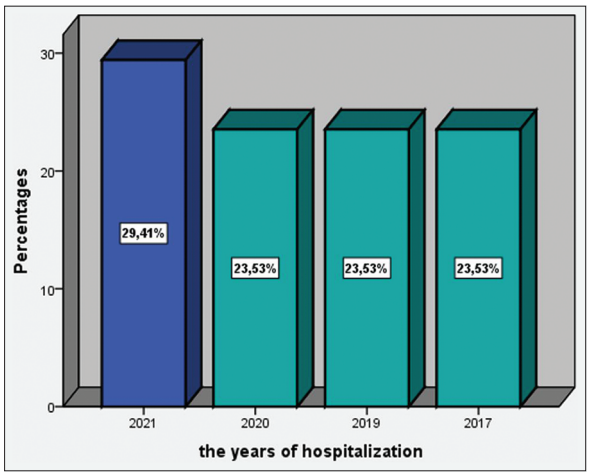

Figure 1: Distribution of toxidermia cases to antiepileptic drugs (%) during the five years of study at the Dermatology Department.

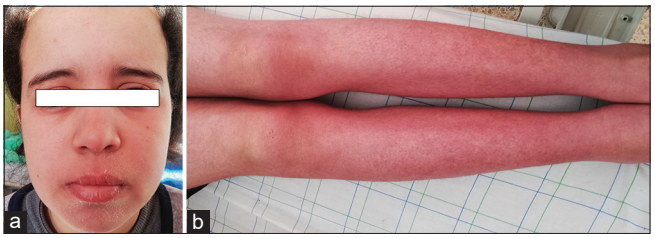

Figure 2: (a and b) Clinical photographs showing an extensive skin rash after the onset of carbamazepine for epilepsy. This patient had DRESS syndrome to carbamazepine.

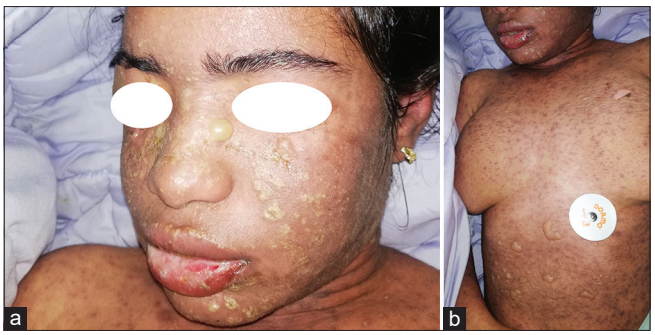

Figure 3: (a and b) Extensive macular and bullous lesions with a positive Nikolski sign and oropharyngeal involvement in toxic epidermal necrolysis induced by carbamazepine in the same patient.

Table 1: Distribution of cutaneous adverse reactions to antiepileptic drugs (CADRs) in our study

Type of CADR	Total cases (%)
DRESS syndrome	9 (52.9%)
Stevens–Johnson syndrome	4 (23.5%)
Toxic epidermal necrolysis	2 (11.8%)
Acute generalized exanthematous pustulosis	1 (5.9%)
Generalized fixed bullous erythema pigmentosa	1 (5.9%)

Table 2: Distribution of the most implicated antiepileptic drugs in our study

Antiepileptic Drug	Number	Percentage (%)	Valid percentage	Cumulative percentage
carbamazepine	9	52.9	52.9	52.9
lamotrigine	2	11.8	11.8	64.7
phenobarbital	2	11.8	11.8	76.5
sodium valproate	4	23.5	23.5	100.0
Total	17	100.0	100.0	

through a medical prescription and there were no cases of self-medication.

Biologically, a complete blood count was disturbed in 64.7% of the cases, with hypereosinophilia in 35.3%, neutrophilic leukocytosis in 11.8%, and leukopenia in 17.6%. Hydroelectrolytic disorders were noted in 17.6%, renal insufficiency in 5.9%, and hepatic cytolysis in 58.8%. Neurological explorations were indicated in 4 cases (23.5%).

Management of Cutaneous Adverse Reactions Induced by Antiepileptic Drugs (Carads)

CARADs required the withdrawal of the suspected drugs in all patients. An antiseptic was prescribed in 47.1%, dermocorticoids in 41.2%, bathing and emollient in 94.1%, and topical antibiotic in 11.8%. Six patients (35.3%) were treated with oral steroids, and fifteen patients (88.2%) were treated with antihistamines. The patients were given a drug card mentioning the name of the drug which had caused the reaction. The evolution was marked by healing in 15 cases (88.2%) and a transfer to the intensive care unit in 2 cases (11.8%).

DISCUSSION

Hypersensitivity to antiepileptic drugs was first reported in 1934 by Silber and Epstein [3,4]. A cutaneous adverse reaction to an antiepileptic drug occurs in 3% of individuals receiving anticonvulsants [3], and numerous sources indicate that antiepileptic drugs are among the most frequent triggers of serious cutaneous adverse reactions. Phenytoin, phenobarbital, carbamazepine, and lamotrigine are the anticonvulsants most frequently involved in toxidermia [3]. The female predominance in our series was consistent with the literature. The risk factors for toxidermia to anticonvulsants are a history of toxidermia to an antiepileptic drug, which was noted in our study in 11.8%, old age, female sex, ethnic origin, genetic predisposition (HLA), vitamin D deficiency, and the presence of comorbidities.

Toxidermia to antiepileptic drugs (AED) is varied, ranging from mild forms (rash and urticaria) to severe forms (DRESS syndrome, Stevens–Johnson syndrome (SJS), and toxic epidermal necrolysis), with an estimated mortality rate of 10% [5-7]. According to a Korean study by Kyung [8] conducted over ten years (2008–2017) on adverse skin reactions to antiepileptic drugs, a total of 2942 cases were studied, among which 2702 (91.8%) had rash/urticaria, followed by 109 cases (3.7%) with DRESS syndrome, 106 cases (3.6%) with Stevens–Johnson syndrome, and 25 cases (0.85%) with Lyell syndrome; however, in our study, we noticed a predominance of cases of DRESS syndrome (52.9%), followed by Stevens–Johnson syndrome (23.5%), toxic epidermal necrolysis (11.8%), generalized acute exanthematous pustulosis (5.9%), and generalized bullous fixed erythema pigmentosum (5.9%); the absence of benign forms was explained by the nature of our study, which was only interested in severe toxidermia requiring hospitalization. In our study carbamazepine was the most often incriminated anticonvulsant (52.9%), followed by sodium valproate (23.5%), lamotrigine (11.8%), and phenobarbital (11.8%), while in a Korean study by Kyung et al, the most frequent antiepileptic drugs involved in mild and severe toxidermia were lamotrigine (699, 23.8%), valproic acid (677, 23%), carbamazepine (512, 17, 4%), oxcarbazepine (320, 10.9%), levetiracetam (181, 6.2%) and phenytoin (158, 5.4%). The same Korean study found that, in 241 cases of severe toxidermia (DRESS, SJS, and Lyell), the antiepileptic drugs involved were carbamazepine in 117 cases (48.8%), lamotrigine in 57 cases (23.8%), valproic acid in 20 cases (8.3%), phenytoin in 15 cases (6.3%), and oxcarbazepine in 10 cases (4.2%) [8]. According to the study by Kyung et al., DRESS syndrome was the most frequently reported adverse reaction, and carbamazepine was the most common antiepileptic drug in severe toxidermia and lamotrigine in general toxidermia [8].

Most of the allergic reactions induced by antiepileptic drugs are the result of delayed cell-mediated hypersensitivity with the probable involvement of HLA class I and sometimes class II. They are insidious and may appear up to several weeks after the beginning of a new treatment, which makes it particularly difficult to implicate a specific drug in multidrug patients. In this situation, the study of imputability scores makes it possible to formalize the evaluation of the causal link and is an aid for diagnosis and management [2,9].

Risk factors for antiepileptic-induced hypersensitivity include a genetic predisposition (HLA-B*15:02,

HLA-B*3101, HLA-B*44:03, and HLA-B*38:01), a history of an allergic reaction to other aromatic AEDs, the reactivation of latent viruses, such as human herpesvirus, Epstein–Barr virus, or *Cytomegalovirus*, infection with human immunodeficiency virus, the co-administration of antiviral drugs, liver disease, advanced age, and concomitant use of immunosuppressive agents [9-17].

The treatment of toxidermia induced by antiepileptic drugs has not yet been codified. The offending drug must be withdrawn if the patient cannot be monitored safely (cognitive problems, elderly, lack of a carer, etc.). Further use of the suspect drug should be contraindicated in severe toxidermia. Symptomatic treatment consisting of hydroelectrolytic control, nutritional support, local care of mucocutaneous lesions, and the prevention of superinfections is an essential part of treatment. The vital prognosis depends on the severity of the toxidermia, in severe forms in particular (DRESS, Stevens, and Lyell). In the literature, the mortality rate is estimated to be 25-30% for Lyell and 10% for DRESS. In our series, no death was found, yet we noted a transfer to the intensive care unit in 11.8% of the cases.

CONCLUSION

This study highlighted the potential of antiepileptic drugs in inducing serious toxidermia and, therefore, their inclusion must be reasoned. The prescription of anticonvulsants must take into consideration the potential risks for the patient versus the potential benefits. Symptoms that may indicate a reaction to the drug should be carefully discussed with the patient or their caregivers.

Statement of Human and Animal Rights

All the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the 2008 revision of the Declaration of Helsinki of 1975.

Statement of Informed Consent

Informed consent for participation in this study was obtained from all patients.

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Source of Support: This article has no funding source.

Conflict of Interest: The authors have no conflict of interest to declare.